

The American Journal of Medicine

Editor ALEXANDER B. GUTMAN, M. D.

Associate Professor of Medicine, COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK

ADVISORY BOARD

Chairman: WALTER W. PALMER, M.D., Bard Professor Emeritus, Columbia University College of Physicians and Surgeons, New York; DAVID P. BARR, M.D., Professor of Medicine, Cornell University Medical College, New York; ARTHUR L. BLOOMFIELD, M.D., Professor of Medicine, School of Medicine, Stanford University, San Francisco; FRANCIS G. BLAKE, M.D., Sterling Professor of Medicine, Yale University School of Medicine, New Haven; EUGENE A. STEAD, JR., M.D., Professor of Medicine, School of Medicine, Duke University, Durham; JOSEPH T. WEARN, M.D., Professor of Medicine, School of Medicine, Western Reserve University, Cleveland.

ASSOCIATE EDITORS

HERRMAN L. BLUMGART, M.D., *Boston*; HARRY GOLD, M.D., *New York*; A. McGEHEE HARVEY, M.D., *Baltimore*; GEORGE H. HOUCK, M.D., *San Francisco*; CHESTER S. KEEFER, M.D., *Boston*; T. GRIER MILLER, M.D., *Philadelphia*; WALTER L. PALMER, M.D., *Chicago*; OSWALD H. ROBERTSON, M.D., *Chicago*; EPHRAIM SHORR, M.D., *New York*; GEORGE W. THORN, M.D., *Boston*; WILLIAM S. TILLET, M.D., *New York*; ROY H. TURNER, M.D., *New Orleans*; RUSSELL M. WILDER, M.D., *Rochester*; M. M. WINTROBE, M.D., *Salt Lake City*; W. BARRY WOOD, M.D., *St. Louis*; JOHN B. YOUNG, M.D., *Chicago*.

Volume VI
JANUARY TO JUNE
1949

THE YORKE PUBLISHING COMPANY, INC.

NEW YORK

MCMXLIX

COPYRIGHT, 1949
By THE YORKE PUBLISHING COMPANY, INC.
All Rights Reserved

Printed in the United States of America

CONTENTS OF VOLUME VI

ORIGINAL ARTICLES

The Manner of Expressing Serum Protein Values . . .	<i>John B. Youmans . . .</i>	1
The Syndrome of Pulmonary Stenosis with Patent Foramen Ovale	<i>Arthur Selzer . . .</i> <i>William H. Carnes . . .</i> <i>Charles A. Noble, Jr. . .</i> <i>William H. Higgins, Jr . .</i> <i>Robert O. Holmes . . .</i> <i>David G. Greene . . .</i> <i>Eleanor deForest Baldwin . .</i>	3
Pure Congenital Pulmonary Stenosis and Idiopathic Congenital Dilatation of the Pulmonary Artery . . .	<i>Janet Sterling Baldwin . .</i> <i>Aaron Himmelstein . . .</i> <i>Charles E. Roh . . .</i> <i>André Cournand . . .</i> <i>Yale Kneeland, Jr. . . .</i> <i>Harry M. Rose</i> <i>Count Dillon Gibson . . .</i> <i>A. de Vries</i> <i>M. Rachmilewitz</i> <i>M. Schumert</i> <i>Richard Gubner</i> <i>Harry E. Ungerleider . . .</i> <i>Robert Paine</i> <i>John R. Smith</i>	24
Aureomycin in the Treatment of Primary Atypical Pneumonia		41
Pheochromocytoma with Diabetes and Hypertension. Report of Two Cases Cured by Operation		51
Arteriosclerosis. A Statement of the Problem . . .		60
The Mechanism of Heart Failure. A Résumé of Physiologic Factors in Cardiovascular Failure		84
Cholesterol Metabolism and Arteriosclerosis		103
Hepatosplenomegaly, Jaundice, Anemia and Recurrent Fever		125
Spontaneous Hemopneumothorax with Recovery . . .	<i>Virgil J. Dorset</i> <i>Luther L. Terry</i>	135
Coronary Failure and Coronary Arteritis	<i>Arthur L. Bloomfield . . .</i>	139
Multiple Myeloma. Its Clinical and Laboratory Diagnosis with Emphasis on Electrophoretic Abnormalities . .	<i>W. S. Adams</i> <i>E. L. Alling</i> <i>J. S. Lawrence</i>	141
Test for the Presence of the "Hypertensive Diencephalic Syndrome" Using Histamine	<i>Henry A. Schroeder</i> <i>Melvin L. Goldman</i>	162
Treatment of Thromboangiitis Obliterans. Two-year Follow-up after Sympathectomy	<i>William J. Messinger . . .</i> <i>Edmund N. Goodman . . .</i> <i>James C. White</i>	168
Consideration of Glomerular Nephritis in Its Relation to Sulfonamide Sensitivity	<i>R. H. Rigdon</i> <i>W. H. Siddon</i> <i>D. E. Fletcher</i>	177
Chemotherapy of Malignant Disease	<i>Alfred Gellhorn</i> <i>Logan O. Jones</i>	188
The Role of the Cardiac Output in the Mechanisms of Congestive Heart Failure.	<i>Eugene A. Stead, Jr. . . .</i>	232
Household Poisonings		237

Mediastinal Tumor with Gynecomastia and Superior Vena Caval Obstruction	247
An Unusual Case of Clonorchiasis with Marked Eosinophilia and Pulmonary Infiltrations	George E. Cartwright 259
Co-existent Chronic Glanders and Multiple Cystic Ossseous Tuberculosis Treated with Streptomycin	{ C. Ray Womack } 267 E. Buist Wells
Hemochromatosis. Cardiac Failure Associated with Extensive Hemosiderosis of the Myocardium	Howard L. Horns 272
Problems of Hepatic Disease	Franklin M. Hanger 275
Correlation of Liver Function and Liver Structure. Clinical Applications	{ Hans Popper } Frederick Steigmann } 278 Karl A. Meyer Donald D. Kozoll Murray Franklin Laurance W. Kinsell Harry A. Weiss
The Correlation of Hepatic Structure and Function	{ George D. Michaels } 292 John S. Shaver Harry C. Barton, Jr
The Treatment of Hepatic Amebiasis with Chloroquine	Neal J. Conan, Jr. 309
Liver Function during Infectious Mononucleosis	{ John W. Brown } 321 John LeRoy Sims Edward White Jack E. Clifford
Endocrinopathies Associated with Hyperostosis Frontalis Interna	Floyd E. Harding 329
Subacute Bacterial Endocarditis	{ Ruben Snyderman } 336 James S. Tipping
Epidemiology of Syphilis	{ Theodore J. Bauer } 341 Albert P. Iskrant
Transmission of Disease by Transfusion of Blood and Plasma	{ James R. Cantrell } 345 Mark M. Ravitch
Mechanisms of Salt and Water Retention in Heart Failure	Arthur J. Merrill 357
A Case of Duodenal Ulcer with Anxiety Attacks Treated by Psychotherapy	368
Pneumonia and Empyema	375
Western Society for Clinical Research—Abstracts of Papers Presented at the Second Annual Meeting Held in Los Angeles, October 22 and 23, 1948	386
Chiari's Syndrome—Obliterative Endophlebitis of the Hepatic Veins	{ Hilary H. Holmes } 398 George Melcher
New Antibiotics	Chester S. Keefer 405
Aureomycin in Typhus and Brucellosis	{ Vernon Knight } Francisco Ruiz-Sanchez } 407 Amado Ruiz-Sanchez Walsh McDermott

Effect of Streptomycin Therapy on the Bacterial Flora of the Throat	{ <i>C. Phillip Miller</i> <i>Marjorie Bohnhoff</i> }	417
Immunization of Human Beings with Group A Hemolytic Streptococci	{ <i>Lowell A. Rantz</i> <i>Elizabeth Randall</i> <i>Helen H. Rantz</i> }	424
Treatment of Acute Rheumatic Fever with Aspirin. With Special Reference to the Biochemical Changes	{ <i>William S. Hoffman</i> <i>Mark Pomeranc</i> <i>Italo F. Volini</i> <i>Catherine Nobe</i> }	433
Relative Infectivity of Blood and Cerebrospinal Fluid in Secondary Syphilis	{ <i>Chester N. Frazier</i> <i>H. C. Pian</i> }	443
Penicillin in Oil and Beeswax in the Treatment of Syphilis in Clinic Patients	{ <i>Henry Eisenberg</i> <i>Frederick Plotke</i> }	449
Auricular Flutter in Association with Myocardial Infarction. Its Prognosis and Management	<i>John Martin Askey</i>	453
The Role of Tonsillectomy in the Management of Recurrent Streptococcal Sore Throat, Rheumatic Fever and Glomerulonephritis	<i>Max Michael, Jr</i>	462
Pathogenesis of Renal Dysfunction during Congestive Heart Failure	{ <i>Stanley E. Bradley</i> <i>William D. Blake</i> }	470
Ulcerative Colitis		481
Anorexia, Weakness, Prostration and Death		495
American Federation for Clinical Research—Abstracts of Papers Presented at the Eastern Sectional Meeting Held in Philadelphia, December 4, 1948		504
Fulminating Fatal Gout.	{ <i>H. Spitz</i> <i>O. Steinbrocker</i> <i>S. Schwartz</i> <i>M. Schittone</i> }	513
Friedländer's Bacillus Meningitis Treated with Streptomycin	{ <i>Joseph F. Sadusk, Jr.</i> <i>Arnold S. Relman</i> <i>Robert R. Wagner</i> <i>Roy Barnett</i> }	522
Heart Block and Leukemic Cell Infiltration of Interventricular Septum of Heart	{ <i>David T. Dresdale</i> <i>David Spain</i> <i>Florentino Perez-Pina</i> }	530
Foreword	<i>John R. Paul</i>	535
Epidemiology of Poliomyelitis in the Light of Modern Research	<i>Howard A. Howe</i>	537
Viruses of Poliomyelitis	<i>Robert Ward</i>	551
Mechanism of Immunity in Poliomyelitis and Its Bearing on Differentiation of Types	<i>Isabel M. Morgan</i>	556
Histopathologic Basis of Clinical Findings in Poliomyelitis	<i>David Bodian</i>	563
Problems of the Pathologic Physiology of Poliomyelitis	<i>Fritz Buchthal</i>	579
Clinical Aspects of Acute Poliomyelitis	<i>Dorothy M. Horstmann</i>	592
Moist Heat in the Treatment of Poliomyelitis	{ <i>William T. Green</i> <i>Thomas Gucker</i> }	606

Contents

Bulbar Poliomyelitis. Its Mechanism and Treatment	<i>A. B. Baker</i>	614
Care of the After Effects of Poliomyelitis	<i>Robert L. Bennett</i>	620
Public Health Considerations of Poliomyelitis	<i>Joseph G. Molner</i>	628
Adrenal Medullary Tumor (Pheochromocytoma)	<i>Francis N. Hatch</i> <i>Victor Richards</i> <i>Ralph J. Spiegel</i>	633
Treatment of Pernicious Anemia with Crystalline Vitamin B ₁₂	<i>Randolph West</i> <i>Edward H. Reisner, Jr.</i>	643
Cardiac Venous Congestion. Its Causes and Consequences.	<i>John McMichael</i>	651
American Federation for Clinical Research—Abstracts of Papers Presented at the Midwestern Sectional Meeting Held in Chicago, October 28, 1948		662
Weber-Christian Disease	<i>Richard J. Kennedy</i> <i>Louis R. Murphy</i>	672
Synthetic Analgesic Drugs	<i>H. B. van Dyke</i>	681
Modification of the Effects of Immobilization upon Metabolic and Physiologic Functions of Normal Men by the Use of an Oscillating Bed	<i>G. Donald Whedon</i> <i>John E. Deitrick</i> <i>Ephraim Shorr</i>	684
Effect of Vomiting Due to Intestinal Obstruction on the Serum Potassium. Chemical and Electrocardiographic Observations on Fifteen Cases—Preliminary Report	<i>Samuel Bellet</i> <i>Carl S. Nadler</i> <i>Peter C. Gazes</i> <i>Mary Lanning</i>	712
Hemodynamic Studies in Two Cases of Wolff-Parkinson-White Syndrome with Paroxysmal AV Nodal Tachycardia	<i>M. Irené Ferrer</i> <i>Réjane M. Harvey</i> <i>Herbert M. Weiner</i> <i>Richard T. Cathcart</i> <i>André Cournand</i>	725
Studies on Coronary Circulation. V. Quantitative Changes in a Serum Mucoprotein Following the Occurrence of Myocardial Infarction	<i>Benjamin Simkin</i> <i>H. C. Bergman</i> <i>M. Prinzmetal</i>	734
Clinical Value of Serum Polysaccharide Determinations by the Tryptophane-Perchloric Acid Reaction	<i>Harold L. Israel</i> <i>Marie B. Webster</i> <i>Irene E. Maher</i>	745
What Can We Learn from a Medical History?	<i>Carl Binger</i>	751
Fluorocardiography (Electrokymography)	<i>Aldo A. Luisada</i> <i>Felix G. Fleischner</i>	756
Dynamics of Congestive Heart Failure	<i>Dickinson W. Richards, Jr.</i>	772
Rheumatic Heart Disease with Respiratory Failure		781
Gastric Alkalosis with Hypokalemia	<i>Thomas J. Kennedy Jr.</i> <i>John H. Winkley</i> <i>Marcelle F. Dunning</i>	790
Cardiopulmonary Function Studies in a Patient with Ligation of the Left Pulmonary Artery	<i>Charles E. Roh</i> <i>David G. Greene</i> <i>Aaron Himmelstein</i> <i>George H. Humphreys III</i> <i>Eleanor DeF. Baldwin</i>	795

Editorial

The Manner of Expressing Serum Protein Values

NOT infrequently in medicine the early manner of expressing the value or result of a test becomes established by custom and persists long after it has outlived its usefulness, no longer reflects the true meaning of the determination or is actually misleading. A classic example is the content or concentration of hemoglobin in the blood which still continues in many instances to be expressed in percentages of a theoretic and misleading normal rather than in terms of the actual amount per unit of blood even though often determined on that basis.

Another and more recent example is that of serum or plasma proteins. Analysis of serum or plasma for protein usually includes a determination of the total protein and the albumin fraction, the globulin fraction being determined by difference between total protein and albumin. Occasionally, the fibrinogen is determined also. Values are expressed as Gm. of total protein per 100 cc. of serum or plasma, Gm. of albumin and Gm. of globulin. Commonly, another value is expressed, namely, the ratio of albumin to globulin or the A/G ratio. Unfortunately, too often the total protein value and the A/G ratio alone are given, with the expression A/G ratio "normal" or A/G ratio "reversed," without the actual value for the albumin and globulin. This is particularly apt to occur in the publication of the results of clinical research, in case

reports and in the presentation of patients and case records at ward rounds, clinical pathologic conferences and other teaching exercises. In addition to the simple error of omission committed by this procedure, it indicates on the part of the user a lack of proper appreciation of the true value and meaning of this determination or test.

As is well known, the albumin portion of the serum or plasma protein normally constitutes about three-quarters of the total, so that the ratio of albumin to globulin is in the neighborhood of 2:1 or 3:1. In the earlier days of determination of the plasma or serum proteins the increase in globulin to amounts equal to that of the albumin or even greater was observed and constituted an obvious abnormality which attracted considerable attention. From this, then, arose the interest in the ratio between the two fractions, and the custom of expressing the results of the determination in terms of the "ratio" rather than the actual amounts of albumin and globulin.

Such emphasis on the ratio of albumin to globulin is incorrect and improper because it leads to neglect of the actual values for albumin and globulin, both in thought and expression. While alterations in the ratio are significant, the actual concentrations of albumin and globulin are much more important. They have not only more meaning but a different meaning. The reason for this is clear. The amount of

albumin can vary up or down independently of the globulin as the result of any one of a number of abnormal conditions. The same is true of globulin in relation to albumin. The total protein is a resultant of the sum of the albumin and globulin. It, therefore, varies up or down or may even fail to change, despite the presence of abnormalities affecting the amounts of albumin, globulin or both, depending on the magnitude and direction of such change. A reversal of the albumin/globulin ratio with an albumin of 4.5 Gm. and a globulin of 6.0 Gm., as may occur in lymphopathia venereum, has a meaning much different from a reversal of the ratio with an albumin of 1.5 Gm. and globulin of 3.0 Gm. such as may be found in nephrosis. In the former instance the albumin is normal but the globulin considerably increased. In the second instance the albumin is greatly reduced but the globulin is normal. In both instances the albumin/globulin ratio is reversed, but the significance and meaning of the reversal are entirely different.

The examples cited are rather gross. There are other situations in which the variations and their meanings are much more subtle. There is, for instance, the slightly elevated globulin in some cases of nutritional hypoproteinemia which may mask a slight but significant hypo-albuminemia if attention is paid only to totals and ratios. There is the effect of infection on the globulin which causes the same error. The hypo-albuminemia of mild liver disease may be missed unless the amounts of the

two fractions are known, and decreases in albumin may in turn hide from view a significant increase in the globulin.

It can be seen clearly, then, that from this point of view the most important clinical aspect of the serum proteins is the amount or concentration of the two fractions, and that the ratio of albumin to globulin, while interesting, is of much less importance and may be actually misleading unless one knows or is told the amounts of the two protein fractions. In particular, this is true of the globulin. It, more than albumin, is subject to deviations in both directions from the normal. Changes in it, especially excesses, may provide an important clue to some of the more unusual and uncommon diseases, otherwise less likely to be suspected. Increases in the globulin fraction occurring with decreases in the albumin not infrequently mask the latter, without affecting the total protein.

In conclusion, it should be emphasized that while the improper recording or presentation of the results of serum protein determinations, with emphasis on the albumin/globulin ratio, has immediate, practical disadvantages, its most serious effect is on the habit of mind in relation to the diagnostic use of this test. The writer has repeatedly observed failure to recognize or consider diagnostic possibilities based on serum protein determinations because attention was paid to the albumin/globulin ratio only and not to the amounts of individual fractions.

JOHN B. YOUMANS, M.D.

The Syndrome of Pulmonary Stenosis with Patent Foramen Ovale*

ARTHUR SELZER, M.D., WILLIAM H. CARNES, M.D., CHARLES A. NOBLE, JR., M.D., WILLIAM H. HIGGINS, JR., M.D. and ROBERT O. HOLMES, M.D.

San Francisco, California

THE demonstration by Blalock and Taussig¹ that persistent cyanosis in certain types of congenital cardiac disease can be reduced dramatically by a surgical operation has brought into focus the great practical importance of correct clinical diagnosis of congenital cardiovascular malformations. The great interest in congenital heart disease which has developed in the last decade has therefore shifted recently from the non-cyanotic to the cyanotic group.

A considerable number of malformations of the cardiovascular system are associated with cyanosis. Many of these are not compatible with life for more than a few days or months. A small number of the patients survive until childhood and only very few reach adult life. Maude Abbott² stated that nine-tenths of the cases of morbus ceruleus in adults were cases of the tetralogy of Fallot. In the last few years the variation of the tetralogy of Fallot described by Eisenmenger³ has aroused interest and has been accepted as a clinically recognizable entity. In 1945 Currens, Kinney and White⁴ reported eleven cases of still another cyanotic congenital cardiac lesion, namely, pulmonary stenosis with intact interventricular septum and summarized the clinical findings but no consistent diagnostic criteria were established.

Recently we have had the opportunity to observe two cases of pulmonary stenosis with

intact interventricular septum and patency of the foramen ovale in adults. The striking similarity of these cases and the fact that neither of them was diagnosed correctly during life prompted us to review similar cases reported in the literature. The findings in all the available autopsied cases have been summarized and contrasted with the clinical and pathologic features of similar congenital cardiac lesions.

CASE REPORTS

CASE 1. W. H. J., a thirty-nine year old white male, entered Stanford University Hospitals on April 24, 1946, because of increasing dyspnea. His past history revealed that there was some question as to whether or not he was a "blue baby" but his early development was normal. At the age of seven he became somewhat dyspneic upon exertion but played normally. At the age of twelve he was forced to drop out of games. In high school he attempted to play football but was unable to do so because of dyspnea.

He never noticed cyanosis until the age of eighteen when he developed slight cyanosis while swimming. During the third decade of life cyanosis was very mild, mostly noticeable upon exertion and he led a relatively normal life working as a tool grinder. At thirty-one there was slight intensification of cyanosis; at thirty-four cyanosis became moderately severe and his activities were markedly curtailed because of dyspnea. This state of affairs was gradually intensified in severity until he was

* From the Departments of Medicine and Pathology, Stanford University School of Medicine, the Divisions of Medicine and Pathology, University of California Medical School and the San Francisco Hospital (Department of Public Health, City and County of San Francisco).

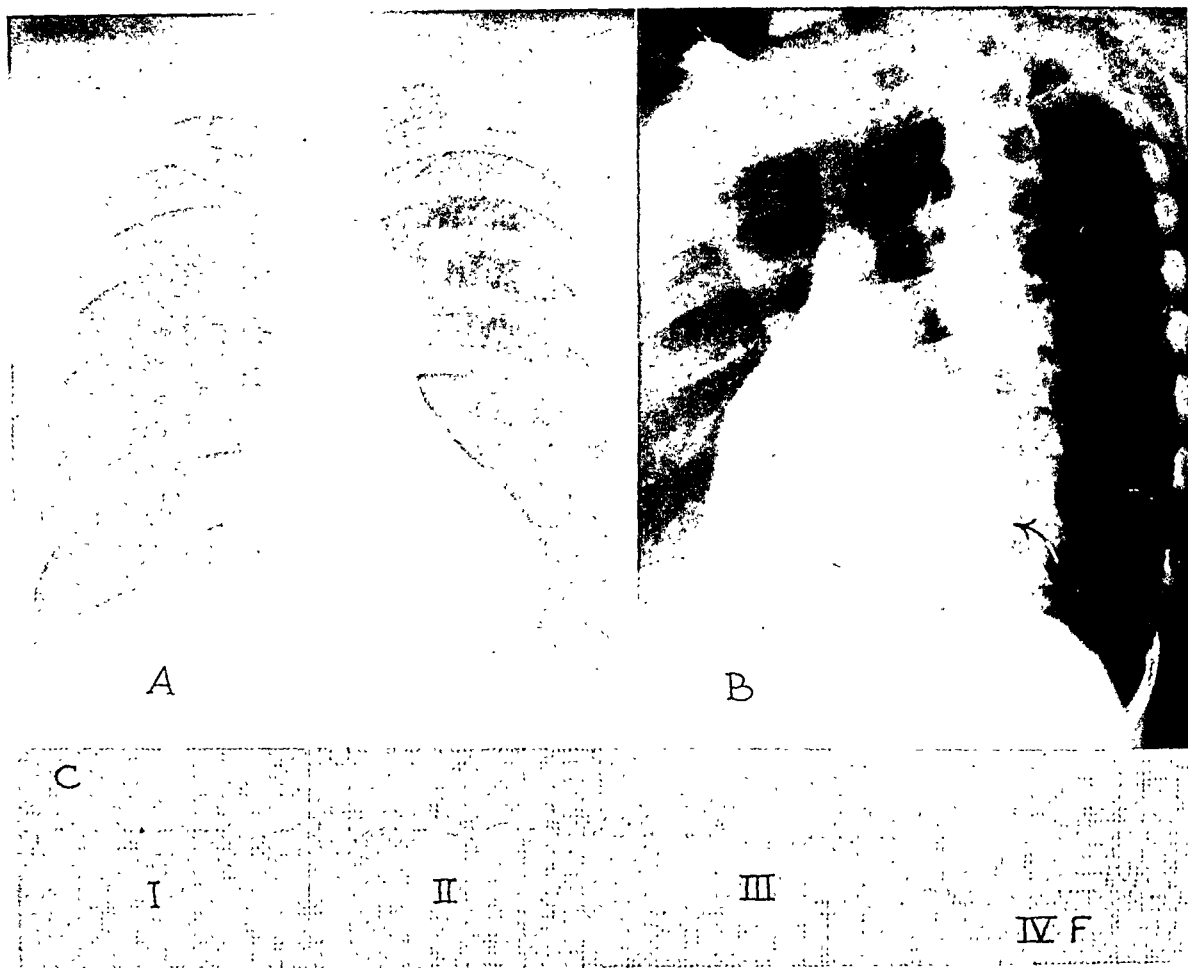


FIG. 1. Roentgenograms and electrocardiogram in Case 1. A, postero-anterior view showing slight cardiac enlargement, dilatation of the pulmonary artery and marked dilatation of the left branch. B, left anterior oblique view showing elevation of the apex and a notch indicating the interventricular groove (arrow). C, four-lead electrocardiogram showing prominent P-waves and a pattern of right bundle-branch block.

completely incapacitated and cyanosis became extreme.

Two years before death he developed attacks of vertigo, with nausea, vomiting and occasional hematemesis. He had few questionable convulsions during the last year. About six weeks before death he was bronchoscoped because of marked enlargement of the left hilar shadow in the chest roentgenogram, suspected as representing a possible tumor, and was found to have partial constriction of the left main bronchus from outside pressure.

Examination upon entry to the hospital revealed an extremely cyanotic man with marked clubbing of the fingers and toes. Other pertinent findings included slight cardiac enlargement with a moderately loud systolic murmur at the apical region, somewhat softer at the left sternal border, and faint at the base of the heart.

The heart sounds were not remarkable, but both were rather loud and snapping at the base of the heart in a sitting position.

Laboratory findings were as follows: vital capacity, varied between 3.5 and 4 L.; venous pressure, 9 cm. of water, circulation time (arm to tongue) 12 seconds. Blood count: hemoglobin, 189 per cent, red blood cells, 9.4 million, leukocytes, 9,500 with a normal distribution. Urinalysis revealed slight albuminuria, pH 5.5, specific gravity 1.007 and occasional leukocytes and rare erythrocytes in the sediment.

Electrocardiogram showed right axis deviation with QRS complexes widened to 0.11 seconds and notched in all leads. T waves were inverted in leads III and IV_F. There was a tall and prominent P₂. (Fig. 1c.) Chest roentgenogram revealed a normal-sized heart with a somewhat elevated apex of the heart and a

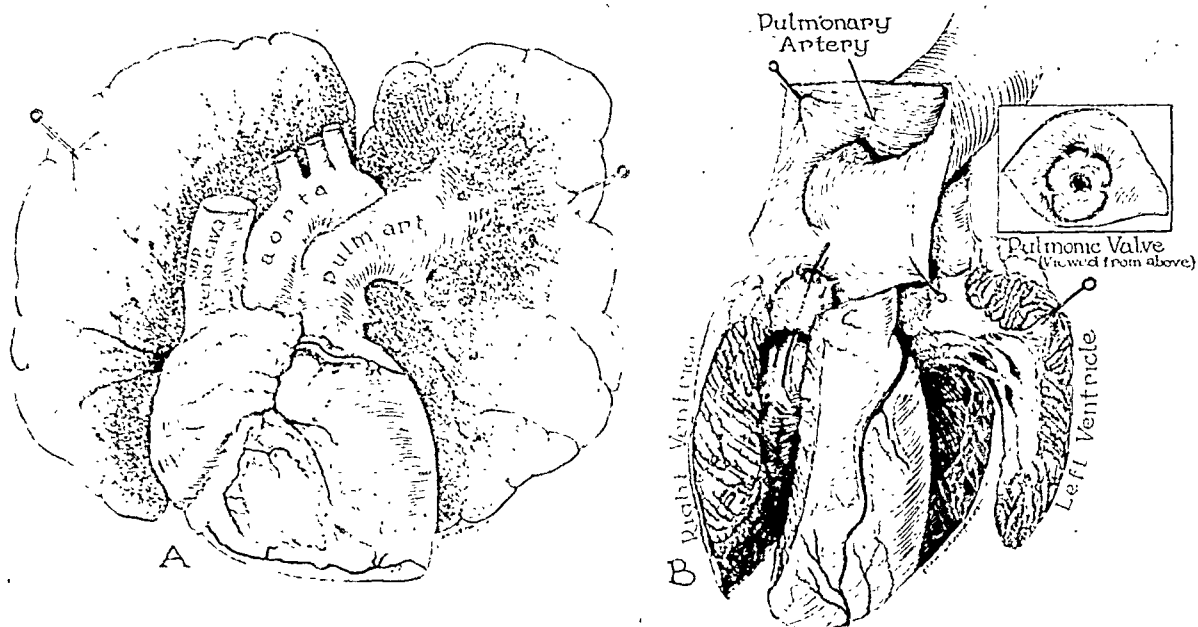


FIG. 2. Drawing of the heart and great vessels in Case 1. A, anterior view of the heart and lungs showing position of the heart and the dilated pulmonary artery. B, section of the heart showing the thickness of the two ventricles and the dilated pulmonary artery. *Inset* upper right hand corner, pulmonary valve seen from above.

marked enlargement of the pulmonary artery and its left branch. (Fig. 1A.) In the left anterior oblique position the apex of the heart showed a notch, suggesting the interventricular groove and thus showing that it was formed mostly by the right ventricle. (Fig. 1B, arrow.)

The patient had repeated attacks of more severe cyanosis with dyspnea. In one of these attacks, on the fourth day after admission, he became irrational and then lapsed into a coma and died.

At autopsy it was revealed that the head, mucosae and upper chest were deep blue. The fingers were moderately clubbed and the nail beds blue. The toes were not clubbed. There was no palpable subcutaneous edema. The serosal surfaces of the abdominal, thoracic and pericardial cavities were normal and there was no fluid in the cavities. The liver edge did not descend below the costal margin.

The heart lay more nearly transversely in the thorax than normally. The entire visible surface from the anterior view was formed by the right ventricle and atrium. (Fig. 2A.) The right atrium was markedly dilated. The right ventricle was dilated and markedly hypertrophied. Its wall measured 18 mm. thick in the conus region. The foramen ovale was covered by the usual endocardial flap, the left margin of which was free so that a round probe 1.5 cm. in

diameter could be passed through it. The tricuspid ring measured 12.9 cm. An interrupted row of small, pale vegetations about 1 mm. wide was found along the line of closure of the tricuspid leaflets and there was an appreciable thickening of the leaflets and several chordae tendineae. The mural endocardium of both the atrium and the ventricle was smooth and thin. The pulmonic valve was extremely stenosed. (Fig. 2B.) It was composed of a dome-shaped, stiff, white membrane with a tiny, round orifice between 2 and 3 mm. in diameter. A continuous row of tiny, pink, translucent vegetations lined the free margin of this orifice. There were no distinct separate cusps but four distinct thin commissures joined the membrane to the base of the pulmonary artery. The pulmonic valve ring had a circumference of 5 cm. The pulmonary artery dilated gradually from the valve ring to the bifurcation and its wall became much thinner in the distal end but the intima was smooth and normal. The dilatation extended into the left main branch of the pulmonary artery giving rise to an aneurysmal sac in the left hilar region corresponding to the shadow in the x-ray film. (Fig. 1A.) The wall of this dilated artery was thin and the intima perfectly smooth but for the wrinkles produced by its collapse when emptied. The vessel was perfectly elastic. There was only a small plaque

in the intima of the artery 2.4 cm. distal to its origin marking the former orifice of the ductus arteriosus. The dilatation did not extend into the secondary branches of the pulmonary artery. The right main branch of the pulmonary artery was about one-half the diameter of the left and appeared normal.

The pulmonary veins emptied normally into the left atrium. There was no enlargement of the left atrium or ventricle. The mitral valve appeared normal and its ring measured 8.7 cm. The left ventricle was 10 mm. thick. The mural endocardium was smooth; the aortic valve appeared normal. Its ring measured 7.2 cm. The myocardium had a normal color and appearance except for a small white scar near the apex of the left ventricle. The coronary arteries were free of sclerosis.

The ascending aorta contained a few very thin yellow intimal plaques. A small yellowish-white plaque in the arch marked the former orifice of the ductus arteriosus. A thin, short ligamentum arteriosum, without a lumen, joined this to the left pulmonary artery. The left bronchial artery arose just distal to the arch of the aorta by an unusually large orifice about 2 mm. wide. The vessel was tortuous and a little larger than normal. In order to trace its course the lungs, heart and aorta were removed *en bloc*. A thick suspension of bismuth oxychloride was injected under a pressure of 130 mm. of mercury into the cannulated artery. This suspension, which ordinarily does not pass the arterioles, poured profusely out of the left pulmonary artery indicating unusually wide anastomoses.

The lungs weighed 670 Gm. together. They were pale, soft and crepitant. The liver weighed 1,375 Gm. and its cut surface showed patchy lobular atrophy and hyperemia. The spleen weighed 255 Gm. and was very firm and almost black. The kidneys weighed 340 Gm. together and were similarly very dark and hyperemic. The organs and tissues generally were all suffused. The bone marrow of ribs, sternum, vertebra and femur were uniformly deep red.

Histologic examination showed that the myocardium contained distinct perivascular cuffs of fibrosis, particularly in the interventricular septum. The myocardial fibers of the right ventricle were thickened. The small scar in the left ventricle was composed of old hyalinized collagenous tissue containing many small thick-walled vessels. The coronary arteries

generally were delicate. The pulmonic valve was markedly thickened, due principally to increased thickness of the central stratum which was hyalinized and contained a fine, dust-like basophilic deposit of calcification. Tiny thin-walled vessels extended through this layer almost to the free margin of the valve which was surmounted by a small, acidophilic, hyaline, amorphous deposit that contained no cells. The tricuspid valve also contained a number of small, thin-walled vessels and small, amorphous, acidophilic deposits on its line of closure which were virtually acellular. The mitral valve was moderately vascularized but showed no vegetations. The aortic valve was normal. The aorta contained only very small intimal plaques composed principally of foam cells. The pulmonary artery had a normal structure except that the thickness of the wall in the distal dilated portion was reduced to about one-half that of the proximal portion. A cross section of the ligamentum arteriosum showed a complete obliteration of the lumen by hyalinized fibrous and elastic tissue. The lungs were normal except for the presence of occasional eccentric thickenings of the walls of small arteries. (100 to 200 micra diameter.) The injected radiopaque material could be identified in small bronchial arteries, pulmonary arteries and occasional very dilated capillary vessels in the peribronchial connective tissue and surrounding alveolar walls. There was marked passive congestion of the other viscera.

Comment. This patient presented the fully developed picture of congenital heart disease with persistent cyanosis. Secondary polycythemia and clubbing of the fingers and toes offered objective evidence of chronic anoxia. Cyanosis developed rather late in life and did not interfere with a moderately active life until the age of thirty-four. At that time intensification of dyspnea and cyanosis started the patient on a gradual downhill course, with death at the age of thirty-nine resulting from severe anoxia. From the diagnostic standpoint the confusing clinical factor was the radiologic appearance of the widely dilated pulmonary artery, the left branch of which was at one time mistaken for a lung tumor.

Pathologically, there was a high degree of stenosis of the pulmonary valve with a



FIG. 3. Roentgenograms in Case II. A, postero-anterior view of the heart showing a normal-sized heart with a hypoplastic aorta and prominent pulmonary artery. B, diodrast-cardiogram interpreted as showing the contrast medium filling the superior vena cava, the right auricle and a stream of the contrast material reaching the left auricle through a patent foramen ovale (arrow). (Courtesy of Dr. Earl Miller, Department of Radiology, University of California Hospital.)

peculiar cup-shaped deformity of the fused valves, a dilatation of the pulmonary artery and wide patency of the foramen ovale. There was also evidence of large collateral circulation to the pulmonary branches from the bronchial artery. The right ventricle was severely hypertrophied, but there was no evidence of chronic congestive failure.

CASE II. L. C., a twenty-five year old divorced white woman, entered San Francisco Hospital on January 10, 1947, complaining of dizziness and episodes of fainting on exertion.

She had first been seen in this hospital in August, 1943 because of salpingo-oophoritis, and at that time was also thought to have congenital heart disease and rheumatic heart disease with mitral stenosis and pulmonary insufficiency. She gave a history of having rheumatic fever at four and since then she has had episodes of exertional dyspnea, dizziness and occasional syncope which she attributed to rheumatic heart disease. She was not cyanotic but was found to have clubbing of the fingers which she thought she had had for many years. Her hemoglobin was 15 Gm. and the red blood count was 4.35 million.

She was next seen at the University of California Hospital in November, 1946 because of dyspnea, weakness, dizziness and fainting on exertion. She stated at that time that these symptoms had occurred off and on during her whole life but were occurring with increasing frequency during the previous three months. She was found to have moderate cyanosis and marked clubbing of her fingers and toes. The heart was slightly enlarged to the left, and there was a moderately loud systolic murmur over the entire precordium, best heard in the third intercostal space at the left sternal border which was also radiating to the axilla and the left scapula. The second sound was louder at the pulmonic area than at the aortic. The liver was slightly enlarged and somewhat tender. A blood count revealed a hemoglobin of 16.6 Gm. and 6.5 million erythrocytes. An electrocardiogram showed marked right axis deviation with inverted T waves in leads II, III, and IV_F and a prominent tall P₂. (Fig. 4A.) Roentgen examination of the chest revealed the heart to be within normal limits of size with a prominent shadow of the pulmonary artery. (Fig. 3A.) Diodrast cardiography was interpreted as showing an interauricular communication with a right to left flow of the contrast material (Fig.

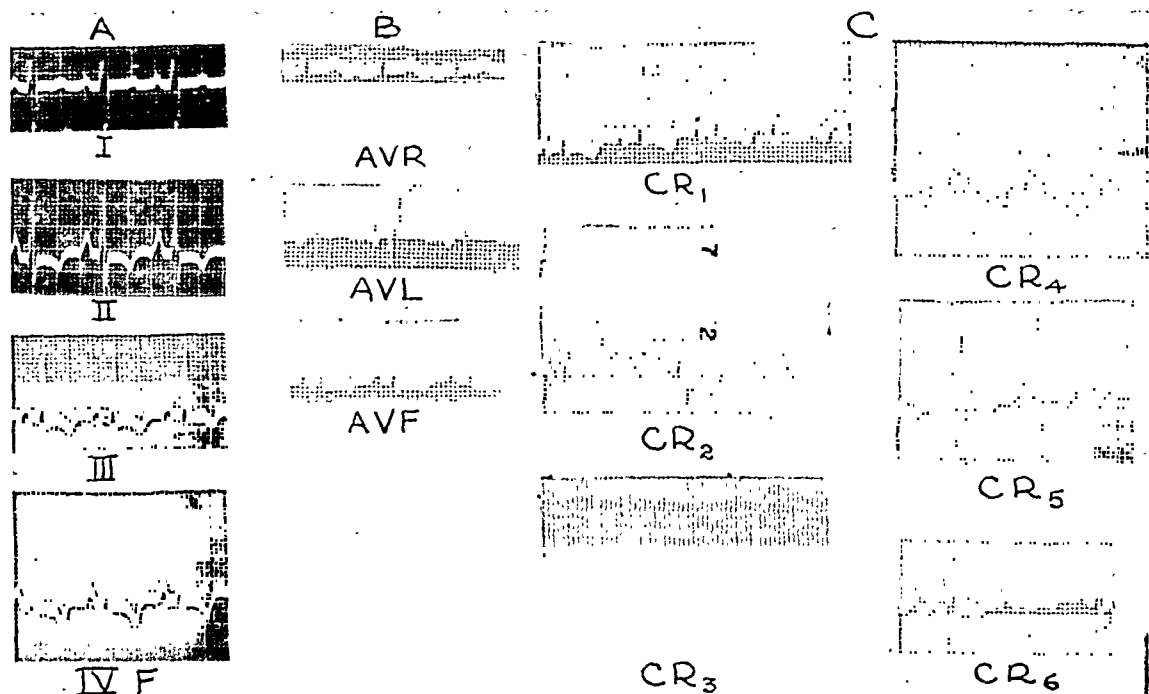


FIG. 4. Electrocardiograms in Case II. A, four-lead electrocardiogram showing the patterns of right ventricular hypertrophy. B, unipolar extremity leads. C, precordial leads, both confirming the diagnosis of right ventricular hypertrophy.

3B), large pulmonary arteries and hypoplasia of the aorta. Diagnosis of congenital heart disease with an interauricular septal defect and hypoplasia of the aorta was made.

Following discharge from the University of California Hospital, the patient continued to have dyspnea, dizziness and fainting episodes with increasing frequency and finally, in January, 1947, reentered the San Francisco Hospital. At that time the cyanosis was found to be severe and she would faint if allowed to stand for a few minutes or upon any exertion. Her blood pressure was 120/90. There was a widely split first heart sound at the apex and a moderately loud, harsh systolic murmur transmitted to the axilla. Another systolic murmur was heard at the second and third left intercostal space. Second sound was present at the pulmonic area. The liver was slightly enlarged; there was no edema. Laboratory studies were essentially negative except for a hemoglobin of 15.9 Gm. and erythrocytes numbering 11 million. The hematocrit reading was 60. An electrocardiogram showed the pattern of right ventricular hypertrophy, essentially as shown in Figure 4A, with additional confirmation of this diagnosis by unipolar extremity leads and leads $v_1 - v_6$. (Fig. 4B.)

Her course in the hospital was slowly but

progressively downhill. She became more markedly cyanotic and dyspneic and fainted on such mild exertion as turning in bed. During the last ten days she developed a low grade fever which was unexplained and she expired on February 6, 1947.

Autopsy was performed seventy-six hours after death by one of us (R. H.) and was limited to examination of the thoracic cavity because of the terms under which consent was granted.

The body was that of a well developed, well nourished, white female measuring 64 inches in length and appearing to be about the stated age of twenty-five years. The weight was approximately 110 pounds. The body showed no edema, but there was well developed post-mortem lividity over its posterior and lateral aspects. There was bilateral clubbing of the fingers and toes.

The right pleural cavity contained 100 cc. of clear, amber-colored fluid, and the left pleural cavity contained 250 cc. of a similar type fluid. The mediastinum was in the midline and small remnants of thymic tissue and fat were present in the superior mediastinum. The pericardial sac contained 50 cc. of clear, amber-colored fluid.

The heart was transverse in position with the anterior surface made up of dilated right auricle



FIG. 5. Photograph of the heart in Case II. A, view of the heart, the stenosed pulmonary valve and the thin-walled, dilated pulmonary artery. B, view of the hypertrophied right auricle and ventricle and the patent foramen ovale (forceps). C, close-up of the pulmonary valve viewed from above.

and enlarged right ventricle. It weighed 330 Gm. and measured 13 by 10.5 by 7 cm. The wall of the right auricle was thickened and on its outer surface were small, fibrous, granular thickenings of the epicardium. The foramen ovale was patent and allowed passage of one finger through the interauricular septum. On the left auricular side was a well developed, thin, fibrous septum with a crescentic opening measuring 1.5 cm. long. The septum covered the opening sufficiently to have acted as a flap valve preventing the flow of blood from the left auricle to the right auricle whereas flow from the right to the left was possible. The left auricle was small and the wall averaged 2 mm. in thickness. The tricuspid valve admitted three fingers with ease and measured 8.5 cm. in circumference. The valve cusps were thickened and there were small warty, pale, greyish-pink vegetations along the margin of closure near the centers of two of the cusps. Some of the chordae tendineae were quite markedly thickened. The wall of the right ventricle was hypertrophied and varied in thickness from 10 to 15 mm. The pulmonary valve showed a complete fusion of all of the free margins of the cusps so that there was a dome-shaped, fibrous diaphragm with a central opening which measured 2 mm. in length and 1 mm. in width. This was the only opening through the pulmonary valve ring. The margins of the opening were fringed with numerous tiny, beaded, translucent, friable, greyish-pink vegetations. (Fig. 5.) The wall of the pulmonary artery was approximately one-third the usual

thickness and the artery was dilated above the valve ring. It measured 2 cm. in diameter just above the valve, and was 3.5 cm. in diameter 2 cm. above the valve ring. In the region of the ductus arteriosus the pulmonary artery was closely approximated to the under surface of the aorta and showed a small dimple in the wall. On the aortic side there was a deeper, funnel-shaped depression which extended obliquely through the wall of the aorta toward the dimple in the pulmonary artery. There was no communication from either side. A large atheromatous plaque was present in the aorta adjacent to the obliterated ductus. The wall of the left ventricle averaged 11 mm. in thickness and the chamber was normal in size. The mitral and aortic valves showed no evidence of disease and were normal in structure. The circumference of the mitral valve was 9 cm. and that of the aortic valve was 6 cm. The aorta was small with a wall of normal thickness. Its circumference was 6 cm. immediately above the aortic ring, 5 cm. 3 cm. above the ring, and 3.9 cm. 6 cm. above the ring. The lower part of the thoracic aorta was 3.5 cm. in circumference. The coronary vessels had a normal distribution and the walls were not thickened.

The right lung weighed 360 Gm. and the left lung weighed 340 Gm. Both lungs were normally aerated and no gross areas of consolidation were present. They were moderately congested but not otherwise unusual upon cut section.

Histologic examination revealed that the myocardial fibers in the right ventricle were

increased in size and were as large as those in the left ventricle. The nuclei were centrally placed and frequently were rectangular in outline. The myofibrils were well preserved but cross striations were indistinct. The majority of the fibers had an increase in the amount of perinuclear pigment, and occasional fibers showed separation of the fibrils. There were occasional small patchy areas of fibrosis between muscle bundles and perivascular fibrosis was also occasionally found. Small foci of lymphocytes and mononuclear cells were present in and adjacent to the fibrous areas. Aschoff bodies were not seen. The cusps of the pulmonary valve were thickened, with the thickest portion midway between the orifice and the attachment, and tapered toward the orifice. The cusps had an increased vascularity with numerous small vessels far out toward the free margin. The thickening was due to the presence of broad hyalin collagenous fibers. The surfaces of the valve were covered with a smooth layer of endothelial cells except at the orifice where the endothelium was interrupted by a proliferation of large, stellate-shaped cells with large hyperchromatic nuclei. These cells showed a slight tendency toward palisading and extended outward for a short distance into masses of fibrin which were adherent to the underlying connective tissue of the cusp. The fibrin was homogeneous and contained very few cells. No bacteria could be demonstrated within the vegetations. The valve cusps attached to the root of the pulmonary artery in a normal manner. The artery above the valve was thin but showed the usual histologic arrangement of elastic fibers. The tricuspid valve was thickened with increases of collagenous connective tissue and blood vessels. Along the margin of closure there was a zone of endothelial ulceration and an adherent fibrinous vegetation similar to those found on the pulmonary valve. The structure of the mitral and aortic valves was normal. Sections through the walls of the aorta and pulmonary artery in the region of the ductus arteriosus showed a short small channel with the lumen obliterated by a completely organized fibrous mass. The aorta had a wall of normal thickness with intact elastic fibers and no evidence of degeneration or inflammation. Sections from several portions of the lungs showed patchy early bronchopneumonia as well as quite pronounced congestion of alveolar capillaries in most regions.

Comment. This patient developed visible cyanosis only a few months before death although clubbing of the fingers and toes was known to have existed for a long time. Cyanosis and polycythemia progressed within a very short time to extreme degrees and the patient died at the age of twenty-five from anoxia. Roentgenologic examination revealed a dilated pulmonary artery and, with the use of diodrast, a defect in the interauricular septum with a right to left blood flow.

Necropsy showed a diaphragm-type stenosis of the pulmonary valve of high degree, a widely patent foramen ovale, marked hypertrophy of the right ventricle and a dilated pulmonary artery. There was evidence suggesting that the ductus arteriosus may have been patent in adult life and obliterated shortly before death. The recent obliteration of the ductus arteriosus may have been the cause of the sudden development and rapid progression of severe cyanosis.

FINDINGS IN CASES TAKEN FROM THE LITERATURE

Maude Abbott's chart of 1,000 cases of congenital heart disease² contains twenty-five cases of pulmonary stenosis with intact interventricular septum.⁵⁻²⁶ Sixteen of these had a patent foramen ovale and in nine the foramen ovale was closed. All but two of these cases have been reviewed and an additional twenty-seven similar cases have been collected from the literature.^{4, 27-40} In order to establish characteristic features for the differential diagnosis of these cases a well documented group of control cases with other congenital lesions and cyanosis has been assembled. This includes twenty-eight cases of proven tetralogy of Fallot⁴¹⁻⁶² and thirteen cases of Eisenmenger complex.^{3, 31, 63-71} Since the primary objective of this report is to establish diagnostic criteria for fully developed clinical entities, the control group was limited to autopsied subjects above fifteen years of age and consisted of Abbott's cases supplemented by more recently reported cases.

Cases of pulmonary stenosis* with intact interventricular septum and patent foramen ovale are presented in some detail. (Table I.) The twenty-three cases of pulmonary stenosis with both septa intact and the control group (twenty-eight cases of the tetralogy of Fallot and thirteen cases of the Eisenmenger complex) have been analyzed and their various clinical and pathologic features compared with those of pulmonary stenosis with patent foramen ovale in Tables II to VII. Special care was exercised in the compilation of the tables to avoid error resulting from the comparison of groups containing children as well as adults with control groups consisting of only those above the age of fifteen. Whenever it was thought that the age may have influenced the incidence of various features, cases of pulmonary stenosis with closed interventricular septum were also limited to those over fifteen in order to make all groups comparable.

Table I summarizes clinical and pathologic findings in patients with pulmonary stenosis with patent foramen ovale and includes twenty-seven cases from the literature and two of our own. The similarities between many of these cases justify separation of this syndrome as a clinical entity not only from the tetralogy of Fallot and the Eisenmenger complex, but from pulmonary stenosis with both septa intact as well. Some of the clinical features of pulmonary stenosis with patent foramen ovale are characteristic enough to make this syndrome a clinically recognizable entity. These features can best be emphasized by comparing this group of cases with others having similar congenital lesions.

Cyanosis. The most important single feature in the diagnosis of congenital heart disease is cyanosis. Cyanosis is the dividing line between various groups of lesions. It is shown conclusively in Table I that pulmonary stenosis with patent foramen ovale belongs to the cyanotic group of congenital

lesions. Table II contrasts the incidence and degree of cyanosis in this syndrome with that in other forms of pulmonary stenosis and in the Eisenmenger complex. The first part of the table shows that pulmonary stenosis with closed foramen ovale is a non-cyanotic lesion with rare exceptions. The contrast between these two forms of pulmonary stenosis has been analyzed in relation to the mechanism of cyanosis elsewhere.⁷² It may be pointed out here, however, that a critical review of the six cases of pulmonary stenosis with closed foramen ovale and cyanosis⁷² reveals that only one of them presented the fully developed picture of chronic cyanosis with secondary polycythemia and clubbing.²⁹ In this case no detailed description of the foramen ovale is presented and an error cannot be ruled out. In the remaining five cases the evidence of persistent cyanosis was not very convincing. On the other hand, in the single case of pulmonary stenosis with patency of the foramen ovale in an adult without cyanosis the foramen was very small. Therefore, it appears that cyanosis in pulmonary stenosis with intact interventricular septum depends on the shunt from the right auricle to the left auricle through the patent foramen ovale.

In the second and third parts of Table II pulmonary stenosis with patent foramen ovale is compared with the tetralogy of Fallot and the Eisenmenger complex. There is no basic difference between the first two types in the degree of cyanosis and the age of onset. Severe cyanosis is infrequent in the Eisenmenger syndrome but the age of onset of cyanosis is similar to that in the other types.

Polycythemia and Clubbing. Secondary polycythemia and clubbing of the fingers and toes offer objective evidence of long-standing arterial anoxemia. Table III shows the incidence of these signs in the four types of congenital heart disease under discussion in cases in which the observations were recorded.

Auscultatory Physical Findings. Auscultation of the heart is an important method of

* Pulmonary stenosis is used hereafter to signify pulmonary stenosis with intact interventricular septum as contrasted with the tetralogy of Fallot.

TABLE I
SUMMARY OF FINDINGS IN TWENTY-NINE CASES OF PULMONARY STENOSIS WITH PATENT FORAMEN OVALE,
ARRANGED IN ORDER OF AGE AT TIME OF DEATH

Case No.	Author	Age, Sex	Physical Signs	Cyanosis	Clubbing	Blood Count	Electrocardiogram	X-Ray	Cause of Death	Heart Weight (Gm.)	Pulmonary Stenosis		Foramen Ovale	Pulmonary Artery	Other Features
											Type	Degree			
1.	Currens 1945 ¹	3 mo. F	Pulmonic systolic murmur; P ₂ diminished	0	0	Normal	Subdural hematoma	..	Stenosis of annulus	1 cm. diameter	Open	Large	Patent ductus arteriosus
2.	Kossman 1942 ¹⁸	4 mo. F	PreCORDIAL systolic murmur	+++	..	R.B.C., 7.7 million Hgb., 22 Gm.	..	Normal heart	Heart failure	..	Dia-phragm	Pinpoint	Open
3.	Tausig 1947 ²¹	7 mo. M	Harsh precordial systolic murmur	+++	Pulmonary conus full	Heart failure	..	Fused cusps forming dome	1.5 mm. diameter	Patent	Moderately dilated	..
4.	Barlow 1878 ¹⁶	4 yr. F	Pulmonic systolic murmur	+	+	Measles	..	Funnel-shaped dome	Small slit	Admits goose quill	Dilated	..
5.	Andrew 1864 ¹³	6 yr. M	Loud pulmonic systolic murmur	+	0	Erysipelas	..	Cup-shaped	Minute aperture	Widely open	..	Ductus arteriosus admits small probe; bicuspid aortic valve
6.	Currens 1945 ¹	11 yr. M	Loud murmur, thrill at base; P ₂ diminished	+	Cerebral abscess	340	Fused valves	Button-hole 9 mm. long	Open 1.1 by 0.3 cm.
7.	Cassell 1891 ¹⁶	11 yr. F	Pulmonic and apical systolic murmurs, P ₂ diminished	Since birth +++	++	Anoxia	..	Cup-like	Round central opening	Open	..	Ductus arteriosus closed
8.	Saundby 1879 ²³	11 yr. M	Systolic and diastolic murmur at base	0	Heart failure	..	Adherent valves forming ring	Round 9 1/8 inch	1 5/16 inch	..	Tiny pulmonic vegetations
9.	Tuley 1917 ²⁵	13 yr. M	Systolic and diastolic murmur and thrill at base	Since 9 yr. +	+	Subacute bacterial endocarditis	350	Fused rings	Admits small probe	5 mm. diameter	Markedly dilated	Massive pulmonic vegetations
10.	Abbott 1923 ¹²	14 yr. F	Moderately loud pulmonic systolic murmur; P ₂ diminished	Progressive since 9 yr. +++	++	R.B.C., 7.6 million Hgb.; 120 per cent	Right axis deviation, tall P waves	Enlarged heart, fullness of pulmonary artery	Anoxia	..	Fused valves forming membrane	Circular opening 2 mm. diameter	Admits pencil	..	Tiny pulmonic vegetations
11.	Gaines 1913 ¹⁸	15 yr. F	Loud pulmonic systolic murmur	0	Tuberculosis	..	Ostium stenosed	8 mm. diameter	2 mm. perforation	Small	..
12.	Currens 1945 ¹	17 yr. M	Moderately loud pulmonic systolic murmur; P ₂ diminished	Mild since 4 yr. +++	++	R.B.C., 8.7 million Hgb., 22 Gm.	Right axis deviation, tall P waves	Enlarged heart and pulmonary artery	Anoxia	380	Fused valves	Oval 6 mm. diameter	..	Moderately dilated	..
13.	Vandam 1947 ²⁰	17 yr. F	Loud pulmonic systolic murmur and thrill	Onset at 2 yr. progressive to +++	++	R.B.C., 10.1 million Hgb., 21 Gm.	Right ventricular hypertrophy	Prominent pulmonary artery non-pulsating	Operation (anec-thesia?)	..	Fused cusps cone-like	2 mm. diameter	Widely patent	Slightly dilated	Large bronchial arteries
14.	Wilks 1858 ²⁶	18 yr. F	Pulmonic systolic murmur	+++	Tuberculosis	..	Funnel shaped diaphragm	4 mm. diameter	2.5 cm. diameter	..	Tiny pulmonic vegetations
15.	Peacock 1848 ²²	20 yr. M	Systolic murmur and thrill, left sternal border; loud P ₂	++	+	Tuberculosis	360	Diaphragm	Triangle admits pencil	6 mm. diameter

TABLE 1 (Continued)

Case No.	Author	Age, Sex	Physical Signs	Cyanosis	Clubbing	Blood Count	Electrocardiogram	X-Ray	Cause of Death	Heart Weight (Gm.)	Pulmonary Stenosis		Foramen Ovale	Pulmonary Artery	Other Features
											Type	Degree			
16.	Auerbach 1947 ²⁹	20 yr. M	Pulmonic systolic murmur	since 17 yr. +++	++	R.B.C., 7.0 million Hgb., 21 Gm.	Right bundle branch block, tall P waves	Normal heart, enlarged pulmonary artery	Pneumonia and heart failure	520	Dia-phragm	2 mm.	1.2 by 0.8 cm.	Normal	Slight tricuspid stenosis
17.	Paul 1871 ³⁷	20 yr. M	Pulmonic systolic murmur and thrill, diastolic murmur	since 7 yr., severe + + +	++	R.B.C., 6.6 million Hgb., 100 per cent			Tuberculosis		Funnel-shaped	Triangle 5 mm.	Widely patent	Aneurysmal dilatation	
18.	Serenini 1925 ³³	21 yr. F	Pulmonic systolic murmur and thrill	++ +					Pulmonary infarct		Cup-shaped membrane	Perforation 4 mm diameter	9 mm diameter	Dilated	
19.	Lafite 1892 ¹⁹	21 yr. F	Pulmonic systolic murmur and thrill	0					Tuberculosis	470	Subvalvular dia-phragm	Triangle 3 mm.	4 mm diameter		Tiny pulmonic vegetations
20.	Niergarth 1889 ²¹	21 yr. M		since infancy + + +				Tuberculosis	215	Funnel-shaped dia-phragm	5 mm. diameter	1 cm. diameter	Small	
21.	Currens 1945 ⁴	22 yr. F	Loud systolic murmur, left sternal border	++ terminally + + +					Heart failure	630	Fused valves		5 mm. by 5 mm.		
22.	McPhedran 1924 ²	23 yr. F	Soft apical systolic murmur, P ₂ diminished	since birth; + + +		R.B.C., 12.5 million Hgb., 140 per cent			Subacute bacterial endocarditis	390	Funnel-shaped	3 mm. diameter	8 mm. diameter		Endocarditis tricuspid valve, tiny pulmonic vegetations
23.	Finlay 1878 ¹⁷	23 yr. F	Loud pulmonic systolic murmur and thrill	since 16 birth + + +	++				Heart failure		Fused valves	5 mm. diameter	1.0 by 1.3 cm.		Ductus arteriosus closed
24.	Our Case 11	25 yr. F	Loud systolic murmur, left sternal border; P ₂ , A ₂ at apex	++ since 24 yr.	since 21 + +	R.B.C., 11.0 million Hgb., 16.6 Gm.	Right axis deviation, tall P waves	Dilated pulmonary artery	Anoxia	330	Funnel-shaped dia-phragm	2 mm. diameter	Large	Dilated	Ductus arteriosus closed, tiny pulmonic vegetations
25.	Currens 1945 ⁴	30 yr. M	Systolic murmur left sternal border; loud P ₂	++ since childhood	R.B.C., 5.8 million Hgb., 90 per cent			Lobar pneumonia	430	Fibrous fusion of valves	Admits pencil	6 mm. diameter	Intraventricular pulmonic branches good size	Tricuspid valve slightly thickened, nodular
26.	Frerichs 1853 ³⁷	34 yr. M	Diastolic murmur left sternal border; P ₂ heard	++					Tuberculosis		Funnel-shaped dia-phragm	Pinpoint	Open	Large	
27.	Our Case 1	39 yr. M	Mild systolic murmur, apex	onset at 18, progressive to + + +	++	R.B.C., 9.4 million Hgb., 188 per cent	Right axis deviation, tall P waves	Dilated pulmonary artery	Anoxia	535	Funnel-shaped dia-phragm	5 mm.	2.1 cm.	Dilated aneurysm-like	Ductus arteriosus closed, tiny pulmonic vegetations, large bronchial arteries
28.	Ballet 1880 ¹⁴	47 yr. F	Precordial murmur and thrill	++				Cerebral abscess		Funnel-shaped dia-phragm	Central hole 5 mm. diameter	Open		
29.	Paul 1871 ³⁷	57 yr. F	Precordial murmur and thrill, P ₂ audible	mild since childhood; + + + after 47				Cerebral abscess	360	Funnel-shaped dia-phragm	Funnel-shaped dia-phragm 5 mm. diameter	Patent		

TABLE II

INCIDENCE, ONSET AND DEGREE OF CYANOSIS IN VARIOUS FORMS OF PULMONARY STENOSIS AND IN THE EISENMENGER COMPLEX

I. Cyanosis in pulmonary stenosis with and without patency of the foramen ovale

	Pulmonary Stenosis with Patent Foramen Ovale	Pulmonary Stenosis with Closed Foramen Ovale
Cyanotic patients		
total number.....	25	6
over the age of 15.....	17	3
Non-cyanotic patients		
total number.....	4	17
over the age of 15.....	1	13

II. Onset of cyanosis in pulmonary stenosis with patent foramen ovale in the tetralogy of Fallot and in the Eisenmenger complex

Age of Onset	Pulmonary Stenosis with Patent Foramen Ovale	Tetralogy of Fallot	Eisenmenger Complex
0-5.....	10	9	4
6-10.....	3	5	2
11-15.....	1
over 16.....	4	4	4
information not available.....	8	10	2

III. Degree of cyanosis during terminal illness

	Pulmonary Stenosis with Patent Foramen Ovale (Patients over 15)	Tetralogy of Fallot	Eisenmenger Complex
None.....	1	1	0
Mild.....	0	2	3
Moderate.....	8	5	8
Severe.....	9	17	1
Total.....	18	25	12

identifying and differentiating various congenital cardiac lesions. It is fully realized that compilation of data from such a heterogeneous group of cases reported by various authors at different periods can only be considered approximate, especially since this is an entirely subjective method of examination. The intensity of the murmurs and their transmission were not commented upon in a sufficient number of cases to warrant inclusion in the discussion. The location of the points of maximum intensity of the murmurs is presented usually as described by the authors, except that murmurs recorded as best heard in the second and third intercostal space at the left sternal border were consolidated with those described as located in the pulmonic area, and murmurs best heard in the third and fourth, or the fourth and fifth intercostal spaces were grouped together as lower left sternal border. Many murmurs were recorded as precordial without better specification and are presented here as such. In order to bring out better the differences in location of the murmurs those with specified location of the maximum intensity were then divided into two groups: (1) those over the upper part and (2) those over the lower part of the cardiac projection of the chest wall. The third intercostal space provided the rough dividing line. No correlation could be found between the location of the murmurs and the type of pulmonary stenosis found at autopsy. The murmurs of valvular and subvalvular stenosis were not distinguishable.

Diastolic murmurs were all described as early diastolic, located to the left of the sternum, except for two cases in which a mitral type of rumbling apical murmur was recorded. It was noted that of the five early diastolic murmurs in the tetralogy of Fallot three subjects were found to have bicuspid pulmonary valves.

In a few cases description of physical findings included comments on the intensity of the second sound at the second left intercostal space. The second sound at that area was described as decreased or absent in five cases of pulmonary stenosis with intact in-

terventricular septum and in one case each of the tetralogy of Fallot and the Eisenmenger complex. On the other hand, it was accentuated in four cases of the former group and in five of the control group. It was noted that in four cases of the tetralogy

TABLE III
INCIDENCE OF POLYCYTHEMIA AND CLUBBING IN PATIENTS
OVER THE AGE OF FIFTEEN

	Pul- monary Stenosis with Fora- men Ovale Closed	Pul- monary Stenosis with Fora- men Ovale Patent	Tetral- ogy of Fallot	Eisen- menger Com- plex
Polycythemia present.....	1	8	9	5
absent.....	6	0	2	0
Clubbing present.....	2	11	17	8
absent.....	8	2	3	2

of Fallot with a normal or loud second sound at the left sternal border the pulmonic valves were not grossly abnormal.

Electrocardiographic Findings. Electrocardiograms were reported in twenty-five of the ninety-three cases. Right axis deviation was, as expected, the prominent feature of all four lesions discussed here. It was present in all but one case and that was a case of the Eisenmenger complex. In four cases right bundle branch block was reported, three of which were cases of pulmonary stenosis with intact interventricular septum and one Eisenmenger complex. In none of these four cases were multiple precordial leads or unipolar leads available to permit a finer differential diagnosis between a true conduction defect and ventricular hypertrophy. Prominent, tall P waves were reported in eleven cases and were less common in the tetralogy of Fallot than in the other two types of pulmonary stenosis. None were reported in the Eisenmenger complex.

Roentgenologic Findings. It is rather difficult to compare the x-ray appearance in a group of patients with so many factors af-

fecting the size, shape and position of the cardiac shadow. However, a review of the data revealed that the most striking feature was the appearance of the pulmonary artery, regardless of the size and shape of the ventricular shadow. Table v shows the

TABLE IV
CARDIAC MURMURS IN VARIOUS FORMS OF PULMONARY
STENOSIS AND THE EISENMENGER COMPLEX

	Pul- monary Stenosis with Fora- men Ovale Closed	Pul- monary Stenosis with Fora- men Ovale Patent	Tetral- ogy of Fallot	Eisen- menger Com- plex
Systolic murmurs				
1. Precordial...	2	4	1	1
2. In upper half of cardiac projection..	15	20	7	3
Pulmonic	11	15	5	3
Area base of the heart...	4	5	2	0
3 In lower half of cardiac projection..	5	3	13	7
Lower left sternal border.....	4	1	12	3
Apical area.	1	2	1	4
Diastolic murmurs....	6	4	5	6
Total: informa- tion available.	22	28	21	11

contract between the x-ray appearance of cases of pulmonary stenosis with and without patency of the foramen ovale and of the tetralogy of Fallot. All patients with pulmonary stenosis, with the exception of one infant, had evidence of dilatation of the pulmonary artery while in the tetralogy of Fallot the pulmonary artery was small in ten cases, questionably enlarged in one case and in one other the cardiac shadow appeared normal. In most cases of pulmonary stenosis the cardiac shadow was not much enlarged so that the two films shown in Figures 1A and 3A can be accepted as representing typical examples of the x-ray ap-

pearance of pulmonary stenosis as judged from the fifteen autopsied cases in which x-ray examinations were reported. In the tetralogy of Fallot, too, the heart was most frequently normal in size. "Sabot"-shaped elevation of the cardiac apex was recorded

TABLE V
ROENTGENOLOGIC SIZE OF THE PULMONARY ARTERY
AND BRANCHES

	Pul- monary Stenosis with Closed Fora- men Ovale	Pul- monary Stenosis with Patent Fora- men Ovale	Tetral- ogy of Fallot	Eisen- menger Com- plex
Prominent pulmonary artery.....	7	7	1 (?)	5
Small pulmonary artery.....	0	0	10	0
Pulmonary artery not remarkable...	0	1	1	0

in some, but not in all cases. In one case there was a right-sided aortic arch. The characteristic deep concavity of the left cardiac border was present even in those with cardiac enlargement, notably in the remarkable case of Volini and Flaxman,⁵⁹ in which the cardiac shadow occupied 80 to 90 per cent of the transverse diameter of the chest and the heart weighed 750 Gm. In the Eisenmenger syndrome the six patients with a record of radiologic examination showed a very characteristic appearance in that the pulmonary artery was very prominent, there was a very marked dilatation of the hilar shadows and the lung fields were intensely congested. Fluoroscopic examination reported in cases of the Eisenmenger complex invariably revealed prominent pulsations of the hilar shadows. In contrast the dilated pulmonary arteries in pulmonary stenosis with intact interventricular septum were usually described as showing absent or slight pulsations.

Course and Prognosis. In spite of the relatively small number of cases analyzed a certain amount of useful information concerning the prognosis of the various lesions can be obtained by comparing the ages attained by the patients and the cause of

TABLE VI
PROGNOSIS OF THE FOUR TYPES OF CONGENITAL HEART
DISEASE

i. Age at death of patients who survived fifteen years
of life

	Pul- monary Stenosis with Closed Fora- men Ovale	Pul- monary Stenosis with Patent Fora- men Ovale	Tetral- ogy of Fallot	Eisen- menger Com- plex
15-20.....	2	6	12	0
21-30.....	6	8	12	4
31-40.....	4	2	2	5
Over 41.....	5	3	2	4

ii. Causes of death in these patients

	3	3	3	9
Heart failure...	1	2	2	0
Anoxia.....	6	1	8	3
Bacterial endocarditis..	1	7	5	0
Pulmonary tuberculosis..	0	3	3	1
Cerebral abscess	5	3	3	0
Other causes...				

death. This is shown in Table vi. Pulmonary stenosis with closed septa and the Eisenmenger complex appear to have a somewhat better prognosis than pulmonary stenosis with patent foramen ovale and the tetralogy of Fallot.

Pathologic Features. The great majority of examples of pulmonary stenosis with intact interventricular septum show strikingly similar anatomic deformities. Of the fifty-one cases forty-three were due to fusion of the cusps. In thirty-two of these the fusion was complete so that a dome-shaped or conical membrane with a small central opening resulted. Sometimes the commissures could be distinguished even when there were no separate cusps as in the two

cases described in this report. In Table VII the types of stenosis are compared in the tetralogy of Fallot and in the two classes of pulmonary stenosis with intact interventricular septum. Valvular fusion occurred in all three classes but it was the nearly exclusive form of stenosis only in the cases with patent foramen ovale and intact interventricular septum. The diaphragm was relatively thin and delicate in some of the youngest subjects but it was thick and rigid in the older patients such as the two reported herein. Histologic examination of the valves was rarely reported except in the presence of bacterial endocarditis. Tiny bland vegetations were often observed on the free margins of the valve orifice. Thickening and mild deformities of the tricuspid valve were frequently noted. The frequent presence of dilatation of the pulmonary artery in those with intact interventricular septum is recorded in the second part of Table VII. The third and fourth parts of the table show that dilatation of the pulmonary artery is directly related to the degree and location of the stenosis.

It is customary to assume that these cases of pulmonary valvular stenosis are congenital. Typical examples have been observed at autopsy in subjects only a few months old and symptoms and signs have been present since birth in many instances. It would be difficult to prove the congenital origin in many cases in adults in whom symptoms appeared late and in whom fibrous thickening and vascularization of the valves so closely resembled the results of rheumatic disease. There are too few reports of careful histologic studies of the heart to provide a basis for generalization on this point. Whatever the pathogenesis of the valvular lesion, the circulatory effects and clinical results would be expected to be the same in all essential respects.

COMMENTS

It appears from the evidence presented that pulmonary stenosis with patency of the foramen ovale is a distinctive entity. Clinically, it is a cyanotic disease and thereby

differs from pulmonary stenosis with closed foramen ovale. This is a fundamental difference which justifies very strict separation of these two conditions which are so often grouped together as "pulmonary stenosis with closed interventricular septum." The striking contrast is best illustrated in adult

TABLE VII
PATHOLOGIC FINDINGS IN VARIOUS TYPES OF PULMONARY STENOSIS

i. Type of pulmonary stenosis

	Pulmonary Stenosis with Closed Foramen Ovale	Pulmonary Stenosis with Patent Foramen Ovale	Tetralogy of Fallot
Valvular fusion, diaphragm type	9	23	2
Valvular fusion, partial	6	5	8
Hypoplasia, pulmonary artery	0	0	8
Subvalvular membrane	2	1	8
Conus separate chamber	5	0	1
Total	29	29	20

ii. Size of pulmonary artery

Small	1	3	9
Normal	2	1	5
Dilated	6	12	5

iii. Relation of the size of pulmonary artery to the type of stenosis

	Valvular Stenosis	Subvalvular Stenosis
Small pulmonary artery	8	4
Dilated pulmonary artery	22	1

iv. Relation of the size of pulmonary artery to the degree of stenosis

	Severe Stenosis	Moderate Stenosis	Mild Stenosis
Small pulmonary artery	0	5	3
Dilated pulmonary artery	12	7	2

patients who, with the same degree and position of pulmonary stenosis, with similar incidence of marked right ventricular hypertrophy and of cardiac failure, develop chronic cyanosis with secondary polycythemia only in the presence of a patent foramen ovale. The cyanosis can only be interpreted as indicative of a large venous-arterial shunt through the foramen ovale. The existence of a right to left shunt has been demonstrated in one of our patients by angiocardiology and in another reported case by cardiac catheterization.³⁰ That such a course of blood flow is compatible with cardiodynamics even in the absence of right ventricular failure and tricuspid insufficiency has been discussed elsewhere in a study of cyanosis.⁷²

In pulmonary stenosis with closed foramen ovale there is no demonstrated cause of chronic cyanosis. Maude Abbott states that in these cases cyanosis is entirely due to capillary stasis but this explanation does not appear very likely. No direct evidence of capillary stasis has ever been presented in pulmonary stenosis without cardiac failure nor have alterations in the velocity and volume of the circulation and in venous pressure been demonstrated. An important argument against such a view is the absence of cyanosis in patients with most marked pulmonary stenosis and cardiac hypertrophy in this series, unless the foramen ovale was patent. A critical review of patients with closed foramen ovale shows that in the few considered cyanotic the evidence is unconvincing. It is not unreasonable to suspect one of three possibilities: (1) cyanosis developed with heart failure and therefore was not different from terminal cyanosis of other cardiac patients, (2) a patent foramen ovale may have been overlooked at autopsy and (3) fetal passages permitting right to left flow may have existed in the past but closed before death. In spite of the fact that Abbott,² Currens, Kinney and White,⁴ Taussig³¹ and others have pointed to the possible rôle of the foramen ovale as a path for an intracardiac shunt this has not been sufficiently emphasized, and the im-

portance of the open foramen ovale in right-sided cardiac lesions is not generally appreciated.

Cyanosis in pulmonary stenosis with patent foramen ovale varies in intensity and may occasionally be absent. In this respect it is not different from the tetralogy of Fallot and the Eisenmenger complex. With any cyanotic lesion, patients may present the picture of morbus ceruleus from birth or may show intermittent cyanosis, late onset of cyanosis or gradual intensification of cyanosis. Pulmonary stenosis with patent foramen ovale occupies an intermediate place between the tetralogy of Fallot, the most severely cyanotic lesion and the Eisenmenger complex, the least cyanotic of the three. It is doubtful, however, whether the degree or time of onset of cyanosis can be used to differentiate these three lesions.

There are no physical signs pathognomonic of pulmonary stenosis. There are, however, important differences between pulmonary stenosis on one hand and the tetralogy of Fallot and the Eisenmenger complex on the other which may be utilized in the diagnosis. In pulmonary stenosis with or without patency of the foramen ovale the systolic murmur is heard in the majority of patients in the pulmonic area whereas with the other two lesions it is more often present along the lower left sternal border. This difference suggests very strongly that the murmur of the tetralogy of Fallot originates in the interventricular septal defect rather than at the site of pulmonary stenosis or, at least, that this represents the more prominent of the two components. As already mentioned no important information could be gained from the description of the intensity of the systolic murmur, its transmission or the presence of thrills. However, the occasional mention of the systolic murmur in the tetralogy of Fallot being conducted to the clavicles and the vessels of the neck suggests the unproven but interesting possibility that such transmission may be a sign of over-riding aorta

and thus evidence against the presence of pulmonary stenosis alone.

Early diastolic murmurs occur most frequently in the Eisenmenger complex at which point they unquestionably represent relative pulmonary insufficiency which is also shown by the marked hilar pulsations. They occur less frequently in the various forms of pulmonary stenosis when they indicate organic pulmonary regurgitation. Because of the anatomic type of the lesion, one might expect an even more frequent occurrence of diastolic murmurs in valvular pulmonary stenosis which accounts for the majority of patients with a closed interventricular septum.

The intensity of the second sound is of limited value in the differential diagnosis. An accentuated second sound along the upper left sternal border most likely indicates absence of pulmonary stenosis or, if the latter is present, subvalvular rather than valvular stenosis. In true valvular stenosis the second sound is often diminished or absent in this area. This relationship, however, is disturbed by the fact that the second heart sound at that location is often transmitted from the aorta as pointed out by Currens et al.⁴ and as shown in some of the cases in our series. It was heard in some patients in whom anatomic changes in the valves made their closure appear impossible.

Electrocardiographic examination does not offer any characteristic information about the type of the lesion for all lesions under discussion are associated with right axis deviation. Prominence of the P waves is more common in pulmonary stenosis than in the tetralogy of Fallot and was not noted in the Eisenmenger syndrome. It may be noted that right bundle branch block appeared in three cases of pulmonary stenosis and in none of the tetralogy of Fallot. This suggests that it indicates a high degree of right ventricular hypertrophy rather than an organic defect of the interventricular bundle which should be more likely to occur in septal defects. Some caution has to be exercised therefore in assuming that con-

duction disturbances are likely to indicate interventricular septal defects.

Roentgenologic examination is by far the most important method in the differential diagnosis of cyanotic congenital lesions. The characteristic x-ray appearance of pulmonary stenosis is due to the post-stenotic dilatation of the pulmonary artery in spite of which the lung fields are more radiolucent than normal. These dilated pulmonary arterial shadows show diminished or absent pulsations. This is in contrast to the small size of the pulmonary vessels in the tetralogy of Fallot with a concave "waistline" of the heart, and the more prominent dilatation of the pulmonary conus, artery and branches with intense pulmonary congestion and increased pulsations in the Eisenmenger complex. The characteristic appearance of the sabot-shaped heart of the tetralogy of Fallot is well known. Comparing pulmonary stenosis and the Eisenmenger complex with the better established roentgen configurations of the non-cyanotic congenital lesion, the former resembles that of a patent ductus arteriosus while the latter presents an almost identical x-ray appearance with an atrial septal defect. The striking uniformity of the x-ray pictures presented in Table VI may be a coincidence. From the pathologic analysis of the series one expects to find an occasional case of the tetralogy of Fallot with poststenotic dilatation of the pulmonary artery or a case of pulmonary stenosis with small pulmonary vessels. Occasional exceptions, however, do not weaken the importance of the characteristic x-ray appearance of the various types of pulmonary stenosis, especially since the differences are well explained by the anatomic findings.

The importance of realizing the frequency of the poststenotic dilatation of the pulmonary artery and its effect upon the radiologic appearance of the heart is emphasized by the practical value of the x-ray in selecting patients for the Blalock-Taussig operation. Reliance upon the size of the large pulmonary branches in the selection

of patients for operation⁷³ would eliminate most of those with pulmonary stenosis with intact interventricular septum. In spite of the very large and dilated pulmonary artery, the appearance of which might make the surgeon hesitant, one may expect pul-

TABLE VIII
SUMMARY OF DIFFERENTIAL DIAGNOSIS IN VARIOUS FORMS
OF PULMONARY STENOSIS AND THE EISENMENGER COMPLEX

	Pulmonary Stenosis with Closed Foramen Ovale	Pulmonary Stenosis with Patent Foramen Ovale	Tetralogy of Fallot	Eisen- menger Complex
Cyanosis	absent	severe	severe	moderate
Clubbing	absent	marked	marked	moderate
Polycythemia	absent	marked	marked	moderate
Systolic murmurs	pulmonic area	pulmonic area	left sternal border	left sternal border
Diastolic murmurs	occasion- ally present	occasion- ally present	occasion- ally present	common
2d sound pulmonary area	often di- minished	often di- minished	variable	loud
Electrocardiogram Right ventricular hypertrophy	prominent	prominent	prominent	mild
P waves	tall	tall	often tall	not re- markable
Röntgenogram Pulmonary artery	enlarged	enlarged	small	markedly enlarged
Hilar shadows	moderate size	moderate size	small	very large, pulsating
Pulmonary congestion	absent	absent	absent	severe

monary stenosis with patent foramen ovale to be aided by the operation as much as the tetralogy of Fallot.⁷²

A summary of findings valuable in the differential diagnosis of the three cyanotic lesions and of pulmonary stenosis with closed foramen ovale is presented in Table VIII. Information presented here is based on probability, indicating the features present in the majority of cases analyzed.

The question of how precise an identification of the lesion can be made by the use of newer diagnostic methods, such as angiocardiology and cardiac catheterization, must be left open. These methods are of great value and are becoming established as most important diagnostic procedures in congenital heart disease. Thus far, too few cases have been reported with autopsy confirmation to know whether a demonstration

of a lesion by one or both of these methods can be considered definite proof of correctness of the diagnosis.

The question of the prognosis of cyanotic cardiac disease cannot be answered with any degree of accuracy from a small series of cases. It is important, however, to note that more patients die as a result of complications than of cardiac failure. This may be interpreted as showing the ability of the heart to carry the burden of the structural deformities for an amazingly long time. It would follow that symptomatic treatment of the cyanosis, such as the Blalock-Taussig operation, is worth while.

Finally, the relative incidence of the three types of cyanotic cardiac lesion deserves some consideration. It is exceedingly difficult to determine the frequency of various lesions for they are too rare for reliable statistics from any institution and the calculations from the number of cases reported in the literature are misleading. Cases are usually reported only if they present some unusual feature so that rare conditions are reported in greater number than more usual ones. It seems probable that pulmonary stenosis with patent foramen ovale is less common than the tetralogy of Fallot and that it is more common than the Eisenmenger complex. The respective incidences of these three main types of cyanotic congenital heart disease in adult life are unknown.

SUMMARY

Two cases of pulmonary stenosis with intact interventricular septum and patency of the foramen ovale are reported, with an analysis of twenty-seven additional autopsied cases from the literature. This series is compared with the reports of autopsied cases of pulmonary stenosis with both septa closed, of the tetralogy of Fallot and of the Eisenmenger syndrome.

Pulmonary stenosis with patent foramen ovale is characterized by chronic cyanosis, polycythemia and clubbing. In the degree of cyanosis it occupies an intermediate place

between the tetralogy of Fallot and the Eisenmenger syndrome. Pulmonary stenosis with closed septa is essentially a non-cyanotic lesion.

On the basis of cyanosis, cases of pulmonary stenosis with and without patency of the foramen ovale are placed in different classes of congenital heart disease. Otherwise these two diseases are clinically and pathologically very similar and differ from the tetralogy of Fallot in important respects.

The most distinctive feature of pulmonary stenosis with patent foramen ovale is the x-ray appearance of the cardiac shadow which is characterized by a poststenotic dilatation of the pulmonary artery and its branches. This again places the condition in an intermediate position between the small shadows of the pulmonary vessels in the tetralogy of Fallot and the very prominently dilated and congested pulmonary vessels of the Eisenmenger syndrome.

Other clinical features and pathologic findings of this lesion are discussed and evidence is presented that it is a well defined clinical entity with enough distinctive features to make possible diagnosis during life. Next to the tetralogy of Fallot it is the most important congenital cardiac lesion in adults with chronic cyanosis, polycythemia and clubbing.

Pulmonary stenosis with patent foramen ovale represents a conspicuous exception to the rule that cyanotic congenital heart disease with dilated pulmonary arteries is unsuitable for surgical relief.

REFERENCES

1. BLALOCK, A. and TAUSSIG, H. B.: The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. *J. A. M. A.*, 128: 189, 1945.
2. ABBOTT, M. E. Congenital Heart Disease. In Nelson's Loose Leaf Medicine. Vol. 4, pp. 207-321. New York, 1932. T. Nelson and Sons.
3. EISENMENGER, V. Die angeborene Defekte der Kammercheidwand des Herzen. *Ztschr. f. klin. Med.*, 32: 1, 1897.
4. CURRENS, J. H., KINNEY, T. D. and WHITE, P. D. Pulmonary stenosis with intact interventricular septum. *Am. Heart J.*, 30: 491, 1945.
5. ABBOTT, M. E. Congenital Heart Disease. In Nelson's Loose Leaf Medicine. Vol. 4, p. 285, 1932.
6. BISHOP, L. F., JR. and WALLACE, S. C. Pulmonary stenosis with bacterial endocarditis in an adult. *Am. Heart J.*, 5: 238, 1929.
7. CLARKE, J. J. A case of ulcerative endocarditis associated with stenosis of the conus arteriosus and affecting chiefly the pulmonary valve, with ulceration of the main pulmonary artery. *Tr. Path. Soc. London*, 44: 29, 1893.
8. HEBB, R. G. Stenosis of pulmonary artery; congenital heart disease. *Tr. Path. Soc. London*, 41: 57, 1890.
9. OGLE, J. W. Abnormal condition of the valve at the root of the pulmonary artery with consequent hypertrophy of the parietes of the right ventricle of the heart. *Tr. Path. Soc. London*, 5: 69, 1854.
10. PEACOCK, T. B. Contraction of the orifice of the pulmonary artery from fusion of the valves. *Tr. Path. Soc. London*, 10: 107, 1859.
11. PEACOCK, T. B. Case of stenosis of the pulmonary artery from disease of the valves, probably of congenital origin. *Tr. Path. Soc. London*, 30: 258, 1879.
12. ABBOTT, M. E., LEWIS, D. S. and BEATTIE, W. W.: Differential study of a case of pulmonary stenosis of inflammatory origin and two cases of (a) pulmonary stenosis and (b) pulmonary atresia of developmental origin with associated ventricular septal defect and death from paradoxical cerebral embolism. *Am. J. M. Sc.*, 165: 636, 1923.
13. ANDREW, J. Congenital malformation of the pulmonary valve. *Tr. Path. Soc. London*, 16: 81, 1865.
14. BALLEZ, G. Des abcès du cerveau consécutifs à certaines malformations cardiaques. *Arch. gén. de méd.*, 1: 659, 1880.
15. BARLOW, T. Congenital heart disease; pulmonary stenosis with dilated pulmonary artery above the stenosis. *Tr. Path. Soc. London*, 30: 272, 1879.
16. CASSELL. *Berl. klin. Wchnschr.*, 28: 1221, 1891.
17. FINLAY, D. W. Malformation of the heart; stenosis of the pulmonary valve, with dilatation of the pulmonary artery and hypertrophy of the right ventricle; patency of the foramen ovale with cribriform opening in the septum of the auricle. *Tr. Path. Soc. London*, 30: 262, 1879.
18. GAINES, L. M. Stenosis of the pulmonary valve of the heart with tuberculosis of the lungs as a secondary and terminal complication. *Charlotte M. J.*, 67: 228, 1913.
19. LAFITTE, A. Rétrécissement infundibulaire de l'artère pulmonaire d'origine congénitale; obliteration incomplete du trou de Botal, absence de cyanose; endocardite végétante au niveau de rétrécissement. *Bull. Soc. anat. de Paris*, 67: 13, 1892.
20. MCPHEDRAN, H. Pulmonary stenosis; patent foramen ovale; acute endocarditis; hemiplegia. *St. Michael's Hosp. M. Bull. (Toronto)*, 1: 62, 1924.
21. NIERGARTH, W. Ein Fall von hochgradiger angeborenen Stenose des Ostium arteriosum dextrum. Tod durch Lungentuberkulose. Munich thesis. 1889.
22. PEACOCK, T. B. Contraction of the orifice of the pulmonary artery and communication between the cavities of the auricles by the foramen ovale. *Tr. Path. Soc. London*, 1: 200, 1848.
23. SAUNDBY, R. Case of pulmonary stenosis with patent foramen ovale. *Brit. M. J.*, 2: 378, 1877.

24. SCREMINI, P. and MONTES-PAREJA, J. Un cas de rétrécissement de l'artère pulmonaire avec propagation du souffle aux vaisseaux du cou sans communication inter-ventriculaire. *Arch. d. mal. du coeur*, 18: 304, 1925.
25. TULEY, H. W. and MOORE, J. W. Report of a case of congenital endocarditis with vegetative inflammation of the pulmonary artery and valve. *Am. J. Dis. Child.*, 13: 426, 1917.
26. WILKS, S. Malformation of the pulmonary veins. *Tr. Path. Soc. London*, 10: 79, 1859.
27. PAUL, C. Du rétrécissement de l'artère pulmonaire. *Bull. Soc. Méd. de Hôp. Paris*, 8: 45, 1871.
28. KOSSMAN, J. I. Congenital atresia and stenosis of great cardiac vessels: aortic atresia, pulmonary stenosis. *Am. J. Dis. Child.*, 64: 872, 1942.
29. AUERBACH, S. H. and HARPER, H. T., JR. Congenital pulmonary stenosis with closed interventricular septum. Report of a case associated with patent foramen ovale and slight tricuspid stenosis. *Am. Heart J.*, 34: 131, 1947.
30. VANDAM, L. D., BING, R. J. and GRAY, F. D. Physiological studies in congenital heart disease. iv. Measurements of the circulation in five selected cases. *Bull. Johns Hopkins Hosp.*, 81: 192, 1947.
31. TAUSSIG, H. B. Congenital Malformations of the Heart. P. 175. New York, 1947. The Commonwealth Fund.
32. ARNETT, J. H. and LONG, C. F. A case of congenital stenosis of the pulmonary valve with late onset of cyanosis; death from carcinoma of the pancreas. *Am. J. M. Sc.*, 182: 212, 1931.
33. EAKIN, W. W. and ABBOTT, M. E.: Stenosis of the pulmonary conus at the lower bulbar orifice (conus a separate chamber) and closed interventricular septum with 2 illustrative cases. *Am. J. M. Sc.*, 186: 860, 1933.
34. BLACKFORD, L. M. and PARKER, F. P. Pulmonary stenosis with bundle branch block. Report of a case with sound tracings and semiserial studies of the conduction bundle. *Arch. Int. Med.*, 67: 1107, 1941.
35. HERTZ, T. Ein Fall von angeborenen Pulmonalstenose ohne anderen Dysplasien und Aplasien mit positivem Denecke'schen Zeichen. *Ztschr. f. Kreislaufforsch.*, 24: 446, 1932.
36. NABERS, L. W. Congenital stenosis of the conus arteriosus with ectasia of the pulmonary artery and bacterial endocarditis of the pulmonary valve. *South. M. J.*, 21: 582, 1928.
37. LEITMANN, G. Eine starke Stenose des Conus arteriosi dextri als Folge einem fibrosen parietalen Endocarditis. *Virchow's Arch. f. path. Anat.*, 267: 290, 1928.
38. GRAHAM, C. S. and GRIFFITHS, E. G. Stenosis of the pulmonary valve. *M. J. Australia*, 1: 51, 1929.
39. GARRISON, R. E. and FELDT, R. H. Congenital pulmonary stenosis with closed cardiac septa: report of a case with comments regarding circulation time. *Am. Heart J.*, 24: 685, 1942.
40. MASSELOT, F., BAUGAS, J. and GIRANDON, C. Rétrécissement infundibulaire et orificiel de l'artère pulmonaire datant de l'enfance avec cyanose apparue à 40 ans. *Rev. Tunis. de Sc. Méd.*, 21: 117, 1927.
41. ANDREWES, F. W. Two specimens of rare forms of congenital malformation of the heart. *Tr. Path. Soc. London*, 54: 144, 1903.
42. BISSELL, W. W. Remarks accompanying a demonstration of two hearts with patent interventricular septum, extensive shortening of the colon and ulceration and huge calculus, dilatation of the ductus pancreaticus Wirsungi. *Tr. Chicago Path. Soc.* 9: 159, 1915.
43. COCHEZ, A. Rétrécissement de l'infundibulum de l'artère pulmonaire et communication interventriculaire sans troubles fonctionnels appréciables jusque l'âge de vingt-six ans; cyanose, tuberculose pulmonaire. *Bull. Soc. med. de Hôp. Paris*, 13: 420, 1896.
44. HERZOG. *München. med. Wchschr.*, 66: 1097, 1919.
45. KURTZ, C. M., SPRAGUE, H. B. and WHITE, P. D. Congenital heart disease; interventricular septal defect with associated anomalies in a series of three cases examined post mortem and a living patient fifty-eight years old with cyanosis and clubbing of fingers. *Am. Heart J.*, 3: 77, 1927.
46. PEACOCK, T. B. Contraction of the pulmonary orifice with imperfection of the septum ventriculorum, and an ossus state of the ductus arteriosus. *Tr. Path. Soc. London*, 7: 80, 1856.
47. PEACOCK, T. B. Great contraction, or stenosis of the pulmonary artery; defect in the septum of the ventricles and aorta arising equally from the two cavities; no ductus arteriosus; but that vessel replaced by two small cavities connected with the aorta. *Tr. Path. Soc. London*, 22: 88, 1871.
48. ROLLESTON, H. Congenital heart disease; pulmonary stenosis; patent septum ventriculorum. *Tr. Path. Soc. London* 43: 32, 1892.
49. WEISS, E. Congenital pulmonary stenosis with ventricular defect. *Tr. Path. Soc. Philadelphia*, 44: 73, 1924.
50. WHITE, P. D. and BOYES, J. H. Subacute bacterial endocarditis and endocarditis involving the tricuspid valve and the pulmonary artery in a unique case of the tetralogy of Fallot complicated by congenital pulmonary regurgitation. *Am. Heart J.*, 7: 802, 1932.
51. WHITE, P. D. and SPRAGUE, H. B. Tetralogy of Fallot; case of a noted musician who lived to his sixtieth year. *J. A. M. A.*, 22, 787, 1929.
52. HARRISON, W. F. Congenital heart disease; extreme congenital pulmonary stenosis; collateral pulmonary circulation; massive right-sided vegetative endocarditis. *Am. Heart J.*, 5: 213, 1929.
53. LECLERC and MICHEL. Rétrécissement pulmonaire; communication interventriculaire; bacilliose pulmonaire. *Lyon méd.*, 122: 300, 1914.
54. MOORE, N. Examples of malformation of the heart. *St. Bart. Hosp. Rep.*, 12: 101, 1876.
55. RAAB, W., WEISS, R., LOWBEER, B. and RÜHL, J. Untersuchungen über einen Fall von congenitalem Herzvitium. *Wien. Arch. f. inn. Med.*, 7: 367, 1924.
56. STONE, W. H. A case of tricoelian heart with insufficiency of the ventricular septum. *St. Thomas Hosp. Rep.*, 11: 57, 1882.
57. TALBOTT, J. H., COOMBS, F. S., CASTELMAN, B., CHAMBERLAIN, F. L., CONSOLAZIO, W. V. and WHITE, P. D. A record case of the tetralogy of

- Fallot with comments on metabolism and pathological studies. *Am. Heart J.*, 22: 754, 1941.
58. SEGALL, H. N. A case of tetralogy of Fallot: clinico-pathological observations, quantitative studies of circulation rate and right to left shunt. *Am. Heart J.*, 8: 628, 1932.
 59. VOLINI, I. F. and FLAXMAN, N. Tetralogy of Fallot; report of a case in a man who lived to his forty-first year. *J. A. M. A.*, 111: 2000, 1938.
 60. CLARKE, N. E. Bacterial endocarditis in congenital heart disease. *J. A. M. A.*, 81: 371, 1923.
 61. PERLMAN, L. and MEYER, J. A case of tetralogy of Fallot with verrucous endocarditis. *Ann. Int. Med.*, 22: 121, 1945.
 62. SCHWEDEL, J. B. Clinical Roentgenology of the Heart. New York, 1946. Paul B. Hoeber. Pp. 324-328.
 63. MILLMAN S. and KORNBLUM, D. Interventricular septal defect with dextraposition of the aorta without stenosis of the pulmonary artery. (Eisenmenger complex) complicated by subacute bacterial endocarditis. *J. Tech. Methods*, 15: 147 1936.
 64. STEWART, H. L. and CRAWFORD, B. L. Congenital heart disease with pulmonary arteritis. *Am. J. Path.* 9: 637, 1933.
 65. SCHRAMM, H. G. Schwere Herzmisbildungen bei älteren Individuen. *Beitr. z. path. Anat. u. z. allg. Path.*, 82: 153, 1929.
 66. ABBOTT, M. E. On the incidence of bacterial inflammatory processes in cardio-vascular defects and in malformed semilunar cusps. *Ann. Clin. Med.*, 4: 189, 1923.
 67. BAUMGARTNER, E. A. and ABBOTT, M. E. Interventricular septal defect with dextraposition of aorta and dilatation of the pulmonary artery (Eisenmenger complex) terminating in cerebral abscess. *Am. J. M. Sc.*, 177: 639, 1929.
 68. TALLEY, J. E. and FOWLER, K. Tetralogy of Fallot (Eisenmenger type) with hypoplasia of the dextraposed aorta. *Am. J. M. Sc.*, 191: 618, 1936.
 69. SAPHIR, O. and LEV, M. The tetralogy of Eisenmenger. *Am. Heart J.* 21: 31, 1941.
 70. DALRYMPLE, J. Diseased heart in which the root of the aorta had an opening common to the 2 ventricles. *Tr. Path. Soc. London*, 1: 58, 1848.
 71. SELZER, A. and LAQUEUR, G. Eisenmenger complex: report of two autopsied cases. To be published.
 72. SELZER, A. and CARNES, W. H. The pathogenesis of persistent cyanosis. To be published.
 73. BLALOCK, A. Physiopathology and surgical treatment of congenital cardiovascular defects. *Bull. New York Acad. Med.*, 22: 57, 1946.

Pure Congenital Pulmonary Stenosis and Idiopathic Congenital Dilatation of the Pulmonary Artery*

DAVID G. GREENE, M.D., ELEANOR DEFOREST BALDWIN, M.D., JANET STERLING BALDWIN, M.D., AARON HIMMELSTEIN, M.D., CHARLES E. ROH, M.D. and
ANDRÉ COURNAND, M.D.

New York, New York

ENLARGEMENT of the pulmonary artery may be associated with any one of a variety of lesions, among which are interauricular septal defects, patency of the ductus arteriosus, mitral stenosis, chronic pulmonary disease, primary pulmonary arteriolar sclerosis and syphilis. Pure congenital pulmonary stenosis with poststenotic dilatation of the artery and idiopathic congenital dilatation of the pulmonary artery without stenosis are two of the less common causes of such enlargement.

During the past two years seven cases of pulmonary artery enlargement have been studied in the cardio-pulmonary laboratories of the Presbyterian Hospital and Bellevue Hospital. The clinical and physiologic diagnosis of pure pulmonary stenosis was made in three cases and of idiopathic dilatation of the pulmonary artery in four cases. One other case of pure pulmonary stenosis without a poststenotic dilatation of the pulmonary artery was also observed. As no attempt was made in either laboratory to make a special study of enlargement of the pulmonary artery the finding of these cases suggests that such congenital malformations are more common than hitherto suspected.

The purpose of this paper is to review the literature on pure congenital pulmonary stenosis and on idiopathic congenital dilatation of the pulmonary artery and to

report the clinical and hemodynamic findings in four cases of each of these two conditions.

PURE CONGENITAL PULMONARY STENOSIS

Pulmonary stenosis is a common congenital heart lesion and one which is compatible with survival to adult life. It is frequently associated with defects of the interventricular septum and dextroposition of the aorta at its origin, the familiar tetralogy of Fallot. Pulmonary stenosis associated with an interauricular septal defect has been reported in a somewhat smaller group of cases.² Pure pulmonary stenosis, i.e., stenosis unassociated with abnormal communications between the greater and lesser circulation, is much rarer. In Maude Abbott's statistical analysis of 1,000 cases of congenital heart disease² pulmonary stenosis associated with a septal defect was found 101 times while pure pulmonary stenosis was found only nine times. In Gibson and Clifton's series of 1,950 autopsies on children under thirteen there were two cases of pure pulmonary stenosis⁵⁸ in a total of just over one hundred cases of congenital heart disease. Only sixty-eight examples of this condition proved by autopsy have been found in the literature.

Table I summarizes the most important findings of these cases. In this series only those cases

* From the Departments of Medicine and Surgery of the College of Physicians and Surgeons, Columbia University; the Department of Pediatrics, New York University and the Cardio-Pulmonary Laboratories of the Presbyterian Hospital and of the Chest Service of Bellevue Hospital, New York, N. Y. This work was supported in part through a grant of the Commonwealth Fund.

TABLE 1

CHIEF CHARACTERISTICS OF SIXTY-EIGHT CASES OF PURE PULMONARY STENOSIS COLLECTED FROM THE LITERATURE

Author	Date	Age	Sex	Edema	Dyspnea	Cyanosis	Systolic Murmur	Systolic Thrill	Right Ventricular Hypertrophy	Infundibular Stenosis	Dilatation of Pulmonary Artery	Pulmonary Tuberculosis	Vegetative Endocarditis	Cause of Death
Philouze ¹⁰⁰	1826	.	M	+	+	.	+	0	0	heart failure
Chelius ³⁰	1827	26	M	+	+	+	+	+	+	.	0	.	.	heart failure
Burnet ²⁴	1830	7	F	+	+	+	+	+	.	.	0	.	.	heart failure
Elliotson ⁵⁰	1830	.	F	+	+	.	+	.	.	+	0	.	.	heart failure
Fallot ⁵³	1834	63	F	+	+	.	.	.	+	.	.	0	0	heart failure
Cruveilhier ³⁶	1835-1842	+	heart failure
Carswell ²⁶	1838	+	tuberculosis
Tiedemann ¹¹⁸	1843	21	M	+	+	+	+	+	+	heart failure
Craigie ³⁵	1843	44	M	.	+	+	.	.	+	.	+	+	.	tuberculosis
Dittrich ⁴¹	1849	20	M	.	.	.	+	+	+	+	0	.	.	heart failure
Ogle ⁹¹	1853-1854	14	F	.	+	.	.	0	+	heart failure
Benedikt et al. ¹²	1854	60	F	+	+	.	+	+	+	.	+	.	.	heart failure
Cejka ²⁹	1855	30	F	+	+	.	+	+	+	.	+	.	.	heart failure, stroke
Bernard ¹²	1856	56	F	+	+	0	+	+	+	+	+	.	.	heart failure, stroke
Peacock ⁹⁷	1859	23	M	.	.	0	+	.	+	.	+	+	.	heart failure, endocarditis
d'Heilly ⁴⁰	1864	21	M	.	+	.	+	.	+	.	+	+	+	scarlet fever
Peacock ⁹⁸	1866	6	F	+	+	+	+	+	+	+	0	.	.	tuberculosis
Meynet ¹⁸	1867	19	F	.	+	.	+	+	+	.	+	+	.	tuberculosis
Paul ^{95,96}	1871	36	M	0	.	0	+	.	+	.	+	+	.	tuberculosis
Solomon ¹¹⁰	1872	31	M	.	.	.	+	.	+	.	+	+	.	tuberculosis
Budin ²²	1873	58	F	+	+	+	+	+	+	.	+	0	0	heart failure
Taruffi ¹¹⁶	1875	21	M	.	+	+	+	+	+	.	+	+	.	tuberculosis
Letouzey ⁸⁵	1877	24	M	.	+	0	+	.	+	.	0	+	0	tuberculosis
Duguet et al. ⁴⁵	1878	24	M	.	+	.	+	.	+	.	+	+	?	tuberculosis
Norman ⁸⁹	1878	26	M	.	.	.	+	.	+	.	+	+	.	sudden
Peacock ⁹⁹	1879	13	M	+	+	+	+	+	+	.	+	0	.	? heart failure, ? peritonitis
Havage ⁶⁴	1879	44	F	+	.	+	+	.	+	.	+	0	.	heart failure
Duguet ⁴⁴	1882	35	F	.	.	.	+	+	+	.	+	0	.	nephritis
Rinsema ¹⁰²	1884	34	M	+	.	0	+	+	+	.	0	0	0	heart failure
Flint ⁵⁴	1884	19	M	.	0	0	+	.	+	scarlet fever
Hebb ⁶⁵	1890	45	M	+	.	.	+	+	+	heart failure
La Fitte ⁷²	1892	21	F	+	+	0	+	+	+	+	0	.	+	vegetative endocarditis
Chrétien ²⁹	1893	19	M	.	.	0	+	+	+	+	0	0	.	sudden
Clarke ²³	1893	21	F	.	+	.	+	+	+	.	.	.	+	vegetative endocarditis
Ormerod ⁹³	1893	24	M	.	.	+	+	.	+	.	.	+	.	tuberculosis
Baric ¹⁹	1895	43	F	.	.	.	+	+	+	+	+	+	.	Addison's disease
Rosenthal ¹⁰⁴	1896	16	M	+	+	+	+	+	+	+	+	0	.	erysipelas
Dresler ^{42,43}	1902-1904	2	F	0	0	0	+	+	+	.	0	0	0	cellulitis
Leclerc et al. ⁶³	1903	27	F	.	.	.	+	+	+	+	+	.	.	heart failure
Arnheim ⁵	1905	5	M	.	+	0	+	+	+	.	+	+	0	heart failure
Josserand ⁷²	1906	22	F	+	+	+	+	0	+	.	+	+	.	heart failure
Genersich ⁵⁷	1907	18	M	.	+	.	+	.	+	+	+	.	.	tuberculosis
Dumas et al. ⁴⁶	1926	23	F	.	0	0	+	.	0	.	+	+	.	tuberculosis
Bishop et al. ¹⁴	1929	32	F	+	+	0	+	mitral	.	.	0	.	+	vegetative endocarditis
Roesler et al. ¹⁰³	1931	46	F	+	+	.	.	.	?	carcinoma
Arnett et al. ⁴	1931	33	M	.	+	+	+	.	.	.	0	0	0	heart failure
Abbott ^{1,2,48}	1932	12	M	+	+	+	+	+	+	+	+	0	0	vegetative endocarditis
Abbott ¹	1932	.	F	+	.	0	.	.	+	+	0	0	+	ruptured appendix
Hertz ⁶⁷	1932	23	M	.	+	+	+	+	+	.	+	+	0	cachexia
Ascarelli ⁶	1932	70	M	+	.	+	.	.	heart failure
Leech ⁸⁴	1935	29½	M	+	.	.	+	.	+	.	+	.	.	heart failure
Bret ¹⁹	1936	70	M	+	.	0	+	.	+	.	+	+	.	heart failure
Patino Mayer ⁹⁴	1936	14	M	0	.	+	+	+	+	.	+	.	+	vegetative endocarditis
Cabrera Calderin et al. ²⁵	1937	11	F	+	+	+	+	+	+	.	+	0	+	vegetative endocarditis
Ash et al. ⁷	1939	14½	F	.	.	0	+	+	+	.	+	.	.	heart failure
Bonamour et al. ¹⁶	1940	75	F	+	+	+	+	+	+	.	+	.	.	heart failure
Blackford et al. ¹⁵	1941	23	M	.	+	+	+	+	+	.	+	0	0	?
Garrison et al. ⁸⁸	1942	16	F	0	+	+	+	+	+	.	0	0	?	?
Currens et al. ³⁷	1945	?
Case II.	1945	5½	F	.	0	0	+	.	+	.	+	0	0	subdural hematoma
Case IV.	45	45	F	.	0	+	+	.	+	.	0	0	0	carcinoma, pellagra
Case VI.	5½	5½	F	.	0	+	+	+	+	.	0	0	+	osteomyelitis, septicemia
Case VII.	5½	5½	M	.	0	+	+	+	+	.	0	0	0	septicemia
Case VIII.	16	16	M	.	+	+	+	+	+	.	0	0	0	heart failure
Case IX.	24	24	F	.	+	0	+	+	+	.	0	+	0	heart failure
Case X.	34	34	F	.	+	0	+	+	+	.	0	0	0	heart failure
Freed et al. ⁵⁵	1946	1½	F	+	0	+	+	+	+	.	+	.	.	heart failure
Lowance et al. ⁸⁶	1948	11	F	+	+	+	+	+	+	.	+	0	0	heart failure
Brook ²⁰	1948	20	F	+	operation

with anatomic confirmation have been collected. Both valvular and infundibular stenosis have been included. No cases with an abnormal communication between the pulmonary and systemic circulations have been used except when the foramen ovale has been described as a functionally closed slit. Most of the valvular lesions are clearly congenital in origin even though some of them were originally erroneously described as acquired.^{81,99} Cases in which vegetative endocarditis is superimposed on an apparently previously normal valve or in which the original valve is destroyed have been excluded.⁶⁹ One case studied with the catheter technic has been omitted because pressures were not recorded in the pulmonary artery and anatomic confirmation was lacking.⁶⁹ Two cases demonstrated by angiocardiology were also omitted for lack of pathologic verification.¹¹³

In the absence of such elaborate studies insistence upon anatomic confirmation is essential, as Routier and Escalle^{51,105-107} have recently demonstrated the inadequacy of the clinical diagnostic criteria of a typical pulmonic systolic murmur and thrill and roentgenologic evidence of pulmonary artery dilatation. Of the eighty-two cases they collected from the literature with this clinical picture only sixteen were found at autopsy to have pure congenital pulmonary stenosis.

Pathologic Findings. Pathologically, pure pulmonary stenosis can be divided into those cases in which the stenosis is at the infundibular area of the right ventricle and those in which the stenosis is at the valve itself.

In the first group the lesion results from an arrest of the normal process which ends in the incorporation of the bulbus cordis in the right ventricle as has been suggested by Keith.⁷³ The right ventricle is divided by a fibrous and muscular ridge into the main chamber and the infundibular portion leading to the pulmonary valve. This latter chamber may be dilated with thick muscular walls or may be a fairly narrow channel. The deformity is usually associated with an interventricular septal defect but seventeen cases were found in which no such defect was present. Five of these showed valvular stenosis as well.

In the second group with the stenosis only at the valve the deformity is strikingly similar in most of the cases. At the usual level of the pulmonary valve there is a diaphragm across the orifice, concave to the ventricle and project-

ing into the root of the pulmonary artery. In the center is a small hole a few mm. in diameter. The lesion has been compared to a cupola, the uterine cervix or to a *musseau de tanche*. The outline of three semilunar valves can be seen in the diaphragm which appears as if it had been formed by the fusion of the edges of the three leaflets. The diaphragm may be fairly thin and pliable or may show some thickening and sclerotic changes. A smaller number of cases do not show the typical cupola but irregularly thickened and deformed leaflets, sometimes only two in number, with an irregular slit between them.

Stenosis of either the infundibulum or the pulmonary valve results in hypertrophy of the right ventricle which was a constant finding when mentioned, in all cases except that of Dumas and Pipard⁴⁶ in which it was specifically mentioned as being absent. At the time of death, particularly with heart failure, the right ventricle may be dilated with resultant tricuspid insufficiency and dilatation and hypertrophy of the right auricle. Sclerotic changes of the tricuspid valve are also frequently noted.

The main pulmonary artery beyond the stenotic valve may be normal in size but in about one-half of the cases it is dilated, sometimes to twice the normal diameter or more. The cause of poststenotic dilatation is not clear. Defective formation of the wall of the pulmonary artery and trophic changes have been suggested but not demonstrated. Cavina²⁵ produced partial pulmonary stenosis in young rabbits by tying a suture around the vessel. At autopsy, after a period of growth, the right ventricle and the pulmonary artery beyond the ligature were found to be much larger than those of controls of the same age. This suggests a mechanical explanation, perhaps associated with turbulent flow. A poststenotic dilatation is sometimes seen in an analogous relation to aortic stenosis.⁶² In lesions such as the tetralogy of Fallot significant dilatation of the pulmonary artery is not common. Here the difference may be in the amount of blood going through the stenotic valve.

Clinical Findings. Frequently the only history given is that of the final illness, and the clinical histories are lacking in some of the cases. Of the sixty-four cases in which the sex of the patient is given thirty-three were females. The most common complaints were those of cardiac dysfunction, edema, dyspnea, palpitations and cyanosis. Some patients, however, suffered no

difficulties from their lesion for many years. In a few it was an incidental finding in the course of an examination for some other condition, particularly tuberculosis. Other patients first noted difficulties with the onset of an associated bacterial endocarditis. Cyanosis was present in twenty-eight of the cases, was specifically mentioned as not being present in eighteen and in twenty-two others was not mentioned at all. A few of the cyanotic patients were blue from early life while in many others cyanosis was noted terminally, perhaps with the onset of congestive failure. One remarkable woman reported by Bonnamour and Dumarest¹⁶ first noted cyanosis at the age of forty. At sixty she began to have dependent edema and died of heart failure at the age of seventy-five. Arnett and Long⁴ report one case of a thirty-three year old man in whom cyanosis first appeared two years before death. It was present in localized areas of the skin and not in the lips or fingernail beds. Arterial oxygen saturation was 94.6 per cent. They attributed the cyanosis in this man to stasis of blood in dilated minute blood vessels of the skin. He died of carcinoma without ever showing evidence of cardiac failure.

Clubbing of the digits was noted in only four cases and was specifically mentioned as absent in ten. Few blood counts are recorded but polycythemia was discovered in three patients and found to be absent in nine.

Examination of the heart shows a systolic murmur which is almost always loudest in the second or third left interspace close to the sternal border. In most cases there is no apparent correlation between the location of the murmur and the presence of infundibular versus valvular stenosis.⁶³ It is usually loud and may obscure the pulmonic second sound. Propagation toward the inner half of the left clavicle and to the interscapular region is usual and has been observed up the vessels of the neck. Propagation to the axilla was noted only once.⁸⁴ Occasionally the Valsalva maneuver results in decreased intensity of the murmur. The second pulmonic sound is usually not described but in nine patients it was softer than usual and in only two was it louder. A systolic thrill in the same area has been found in thirty-six cases. In a few cases a precordial bulge, especially in the pulmonic area, has been noted.

Electrocardiograms were taken in fourteen instances and in eleven of them right axis deviation was noted. In two there was no axis

deviation and in one there was a right bundle branch block. P_1 and P_2 , greater than 1 and 3 mm., respectively as described by Alexander *et al.*,³ were sometimes observed. Of the twelve patients who were examined roentgenologically nine showed enlargement of the middle arc of

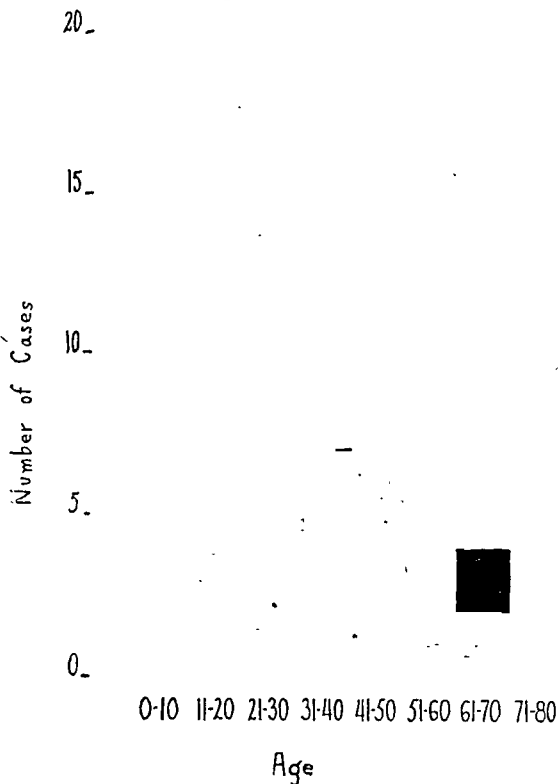


FIG. 1. Age in years at death by decades of sixty-two cases of pure congenital pulmonary stenosis collected from the literature. Brock's patient, who died at twenty, is not included.

the left border of the cardiac silhouette in the postero-anterior position, thought to be due to enlargement of the pulmonary artery. In two of these the enlargement was slight.

Of the sixty-three cases in which the age at death is reported the average length of life was twenty-six years. Figure 1 shows the age at death of this group by decades. Only seven of the patients reached the age of fifty; of these three lived to be seventy. It is thus apparent that the lesion is compatible with survival to adult life but that 89 per cent of the patients die before they reach fifty. Heart failure was the greatest single cause of death, accounting for at least twenty-six of the deaths in this series. Tuberculosis of the lungs was the cause of death in ten and bacterial endocarditis in eight. In six cases the cause of death could not be determined from the data given.

In the older literature the association of pulmonary tuberculosis and pulmonary stenosis was frequently emphasized. Grenet and Francois-Joly⁶⁰ attacked these early figures on the ground that the tuberculosis was not confirmed either radiologically or bacteriologically. Aubertin⁸ found a high incidence of family history of tuberculosis in a series of patients with both lesions. He quotes many opinions on the question, most of which support his view that the coincidence is fortuitous. Auerbach and Stemmerman⁹ found thirteen cases of congenital heart disease in a tuberculosis institution. Of the seven autopsied cases all showed pulmonary stenosis but were also associated with other cardiac anomalies. A review of our series of cases from the literature shows that most of the eighteen cases were from earlier reports at a time when tuberculosis was more common than it is now.

Bacterial endocarditis definitely terminated the course of at least eight of the collected cases and was possibly present in four more. It did not differ from other cases of bacterial endocarditis of the right heart and embolic phenomena in the lungs were frequently present.

The creation of an anastomosis of the Blalock-Taussig type would not be expected to help these patients.¹¹⁷ Their difficulty is not inadequate pulmonary blood flow but rather an abnormal burden on the right ventricle. Valvulotomy in the cases in which the valve alone is involved would seem in theory to be the ideal operation. In the one reported case in which this has been tried²⁰ the patient was in poor condition before surgery and died at operation before the valvulotomy could be performed. Three successful valvulotomies in patients with tetralogy of Fallot indicate, however, that the surgical approach to this area is perfectly feasible.²⁰

PURE CONGENITAL DILATATION OF THE PULMONARY ARTERY

Pathologic Criteria. The pathologic diagnosis of pure congenital dilatation of the pulmonary artery is one which can be made only after various other associated lesions have been eliminated. Septal defects, mitral disease and patency of the ductus arteriosus are obvious lesions which are usually not

overlooked. Other possible causes such as primary pulmonary arteriolar sclerosis and some forms of chronic pulmonary disease are more difficult to eliminate, particularly in incomplete reports. With the usual technic of removal of the heart at autopsy, cutting across the pulmonary artery close to its origin, borderline degrees of dilatation may easily be missed. Therefore, no attempt has been made to exhaust the earlier literature which has been covered in several reviews.^{17,34,38,66} Eight cases with autopsy confirmation have been selected from the literature of the last thirty years as satisfying the following criteria: (1) simple dilatation of the pulmonary trunk, with or without involvement of the rest of the arterial tree; (2) absence of abnormal intra- or extracardiac shunts; (3) absence of chronic cardiac or pulmonary disease, either clinically or at autopsy; (4) absence of arterial disease, such as syphilis or more than minimal atheromatosis or arteriolar sclerosis.

Gold⁵⁹ has restricted the diagnosis of congenital dilatation of the pulmonary artery to cases in which there is concomitant hypoplasia of the aorta. If this is done, even fewer of these cases are acceptable. It would seem, however, that exclusion of a congenital dilatation of the pulmonary artery with an aorta of normal size puts too much emphasis on theoretical developmental grounds. We agree with Gold that the cases of Jennes,⁷¹ Norris,⁹⁰ East⁴⁹ and of DeNavaquez *et al.*³⁹ are not clearly congenital in origin. Gold's own case was not included because of the extensive arteriolar changes described. A few cases have recently been diagnosed during life by the method of angiocardiology^{61,113} but these have not been included.

Clinical Findings. Reference to Table II will show that in the selected cases there were six females and two males with a wide age distribution which included several patients of advanced years. Cyanosis was mentioned as being present three times and absent once. In the three cases in which the pulmonic second sound was described

it was normal once and accentuated twice. Aortic hypoplasia was present in three cases. In one patient the absence of right ventricular hypertrophy was specifically noted. There was one death from pulmonary tuberculosis while the two youngest

there were few or no subjective cardiac complaints. Two young girls complained of dyspnea on exertion but in each case this seemed to bear more relation to anxiety about their hearts than to any functional handicap and in each case it disappeared

TABLE II
CHIEF CHARACTERISTICS OF EIGHT CASES OF IDIOPATHIC DILATATION OF THE PULMONARY ARTERY
COLLECTED FROM THE LITERATURE

Author	Date	No.	Age	Sex	Edema	Dyspnea	Cyanosis	Systolic Murmur	Systolic Thrill	Right Ventricular Hypertrophy	Pulmonary Tuberculosis	Hypoplasia of Aorta
Cautley ²⁷	1920	..	3 1/2	F	..	+	+	+
Sutherland ^{114,115}	1922	..	4	F	+	+	+	+	+	+
Esser ⁵²	1932	..	23	F	+	0
Oppenheimer ⁹²	1933	..	46	M	..	+	+
			60	F	..	+	+	+	..	+
Kourilsky ⁷⁶	1941	4	82	F	0	+
		9	54	M	+	..	0	..	0
Kourilsky ⁷⁶	1942	9	62	F	+	..	0

patients died of congestive heart failure. It is thus apparent that pure congenital dilatation of the pulmonary artery is compatible with survival to middle or old age and that it may produce little functional difficulty.

OBSERVATIONS IN EIGHT CASES

The eight subjects of the present report were children or young adults referred to the cardio-pulmonary laboratories at Bellevue Hospital or to the Presbyterian Hospital for study of congenital heart disease. Beside the usual history, physical examination and electrocardiographic, x-ray and fluoroscopic examinations each patient was studied by the technic of venous catheterization. Anatomic verification is available in Case v in which surgical exploration was carried out. As will be discussed later, however, physiologic studies clearly confirm the diagnosis in each case.

Clinical Findings. The histories of all eight patients were quite similar in that

with reassurance. There was no history in any case of dependent edema or of cyanosis.

Examination showed a chest deformity in two patients. All eight patients had a systolic murmur in the pulmonic area and one had a pulmonic diastolic murmur as well. In four the second pulmonic sound was louder than normal and in one it was diminished. All but one patient showed a prominent pulmonary artery by x-ray. (Figs. 4 to 17.) There were two electrocardiograms which showed right axis deviation. The main findings are tabulated in Table III. The cases have been divided into two groups corresponding to the clinical diagnosis of pulmonary stenosis and pulmonary dilatation. This distinction is based essentially on the results of the physiologic studies.

Physiologic Data. Hemodynamic studies were conducted in each patient using the method of cardiac catheterization. Samples of blood were obtained from the catheter and from an indwelling needle in a systemic

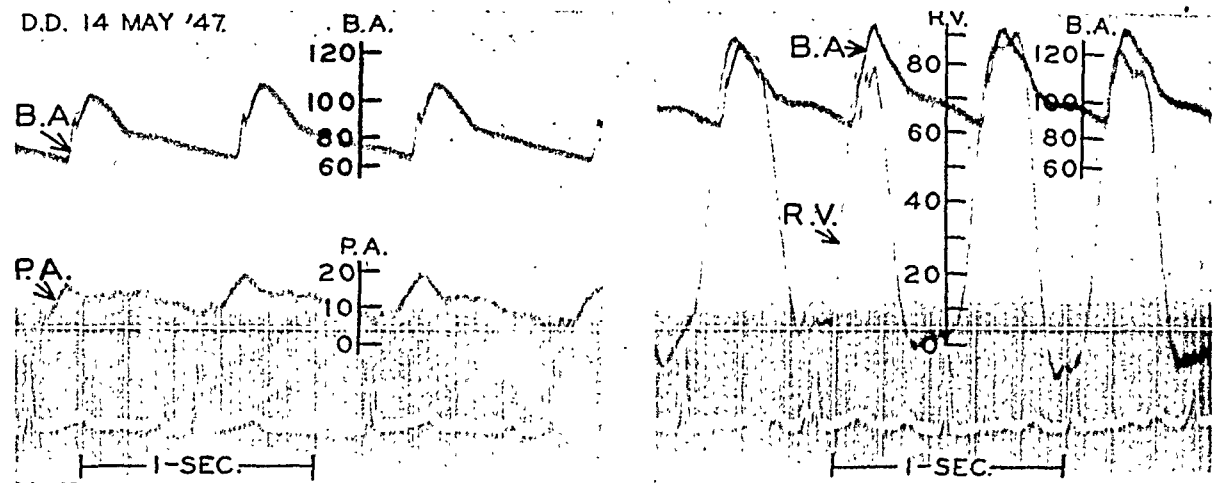


FIG. 2. Pressure tracings in Case 1. Note the low systolic pressure in the pulmonary artery (P.A.) and the high systolic pressure in the right ventricle (R.V.).

artery and were analyzed by the method of Van Slyke and Neill. Expired air was collected in a Tissot gasometer and samples analyzed by the method of Haldane. Pressures were recorded optically with Hamilton manometers. The two youngest patients were studied under rectal avertin anesthesia.

Three patients in this series performed a mild supine exercise after observations at rest had been made. Pressure readings were taken just before the exercise was started and intermittently during and after

exercise. After two to five minutes, while exercise was continued, blood samples and gases were collected for the measurement of cardiac output. In Cases iv and vi the catheter tip was in the right auricle during the exercise and in Case vii it was in the pulmonary artery.

RESULTS

The results of the hemodynamic studies are shown in Tables iv and v. At rest the features common to all eight patients were:

TABLE III
CLINICAL OBSERVATIONS. GROUP I: FOUR CASES OF PURE PULMONARY STENOSIS
GROUP II: FOUR CASES OF IDIOPATHIC DILATATION OF THE PULMONARY ARTERY

Case	Age	Sex	Edema	Dyspnea	Cyanosis	Systolic Murmur	Systolic Thrill	Infundibular Stenosis	Dilatation of Pulmonary Artery	Pulmonary Tuberculosis	Vegetative Endocarditis	Accentuated Pulmonic Second Sound	Right Axis Deviation	Hypoplasia of Aorta
Group I														
I	8	F	0	0	0	+	+	+	+	0	0	—	+	0
II	22	M	0	0	0	+	+	+	+	+	0	n*	0	+
III	15	M	0	0	0	+	+	0	0	0	0	n	0	0
IV	19	M	0	0	0	+	+	..	+	0	0	n	0	0
Group II														
V	17	F	0	0	0	+	0	..	+	0	0	+	0	0
VI	14	F	0	0	0	+	0	..	+	0	0	+	0	+
VII	13	F	0	0	0	+	+	..	+	0	0	+	0	0
VIII	6	F	0	0	0	+	+	..	+	0	0	+	+	0

* n = normal.

(1) constancy within 6 cc. per L. in the individual case of the values for oxygen content of the mixed venous blood samples obtained through the catheter in rapid succession with maintenance of a steady state, (2) normal arterial oxygen saturation,

pressure. In the other seven patients the right auricular mean pressure is normal.

From the oxygen contents of the mixed venous bloods the presence of a left to right shunt can be eliminated. There is no evidence of contamination with oxygenated

TABLE IV
PHYSIOLOGIC OBSERVATIONS. GROUP I: FOUR CASES OF PURE PULMONARY STENOSIS
GROUP II: FOUR CASES OF IDIOPATHIC DILATATION OF THE PULMONARY ARTERY

Case	Oxygen Content of Blood cc./L.						Arterial O ₂ Sat- uration (%)	Cardiac Output (L./ min.)	Cardiac Index (L./ min./ m ² BS)	Pressures (mm. Hg)			
	SVC	IVC	RA	RV	PA	AO				PA	RV	Mean RA	AO
<i>Group I</i> I	112	112	114	152	95	4.78	15/4 22/7 32/17	92/6	1	103/64
II	113	135	126	120	124	172	92	..	2.76	23/10	> 60/12*	8	136/71
III	94	103	100	97	103	129	94	..	5.42	23/13 24/14	59/4 56/6	5	172/87
IV	139	155†	152	149	155	196	96	..	3.40 3.70	18/7 24/7	45/7 48/7	4	135/76 138/76
<i>Group II</i> V	117	116	116	158	98	3.10 4.10	15/0	33/1	-3	130/70‡
VI	121	136	136	134	133	167	99	3.90 4.20	17/4	31/6 28/3	1	126/71
VII	132	139	145	141	146	175	96	3.90 3.88	20/6 16/7	27/4 28/4	2	121/71 138/83
VIII	117	103	112	115	115	156	98	3.10	14/4 15/7	22/2	..	106/60

* Systolic pressure beyond the edge of the recording paper, exact height unknown.

† At entrance of inferior vena cava into right auricle.

‡ Measured by auscultation in arm.

SVC = superior vena cava; IVC = inferior vena cava; RA = right auricle; RV = right ventricle; PA = pulmonary artery; AO = systemic artery; m² BS = square meters body surface.

(3) a significant difference between the right ventricular and pulmonary arterial systolic pressures. (Figs. 2 and 3.) In addition it should be noted that Case II shows evidence of congestive right heart failure as indicated by a high right ventricular diastolic pressure and right auricular mean

blood in any case. In cases I and V no vena caval samples were obtained but the low saturation of the mixed venous blood (less than 75 per cent) rules out a left to right shunt. The normal arterial oxygen saturation in each case eliminates a right to left shunt of any size.

J.P. 9 APRIL '47.

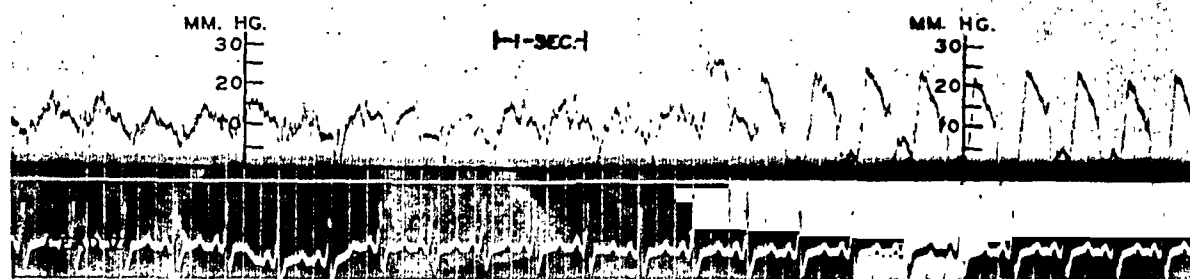


FIG. 3. Pressure tracing taken as the catheter tip was withdrawn from the pulmonary artery into the right ventricle, Case VIII. Note the low systolic pressure in the pulmonary artery and the higher but normal systolic pressure in the right ventricle.

During exercise there were no significant changes noted in the right auricular or pulmonary arterial pressures even though the blood flow increased significantly. All three patients showed an increase in the arteriovenous oxygen difference as well as an increased oxygen consumption. This is a normal response.

Description of the individual cases follows:

CASE REPORTS

CASE I. D. D., an eight year old school girl, was seen at Bellevue Hospital because of a heart murmur which was discovered at the age of six years during her first school examination. She had developed normally and had no complaints except for occasional easy fatigability.

Physical examination showed normal development; there was no clubbing or cyanosis and no dyspnea even after moderately severe exercise. The heart showed slight enlargement to the left. There was a coarse systolic thrill close to the sternum in the third left interspace. The first sound was accentuated at the apex. The second sound was normal in intensity over the aortic area but very faint over the pulmonic area. There was a loud coarse systolic murmur over the upper left precordium which was loudest in the third left interspace at the sternal border and transmitted slightly upward to the left. The blood pressure was 112/72 mm. Hg before exercise, 118/76 mm. Hg after exercise.

Fluoroscopy and roentgenograms (Figs. 4, 5 and 6) showed slight transverse enlargement of the heart, with the apex lifted above the diaphragm. In the region of the pulmonary arc in

TABLE V

PHYSIOLOGIC OBSERVATIONS IN ONE CASE OF PURE PULMONARY STENOSIS AND TWO CASES OF IDIOPATHIC DILATATION OF THE PULMONARY ARTERY—RESPONSE TO SUPINE EXERCISE

Case	State	O ₂ Consumption (cc./min.)	Arteriovenous O ₂ Difference (cc./L.)	Stroke Volume (cc.)	Cardiac Index (L./min./ m ² BS)	Right Auricular Mean Pressure (mm. Hg)	Pulmonary Arterial Mean Pressure (mm. Hg)
IV	Rest	270	44	99	3.4	—	..
	Rest	285	42	94	3.7	3	..
	Exercise	1180	53	174	12.2	3	..
VI	Rest	209	39	61	3.9	—	..
	Rest	224	39	65	4.2	1	..
	Exercise	442	54	71	6.0	0	..
VII	Rest	232	37	58	3.9	..	13
	Rest	231	37	60	3.9	..	10
	Exercise	614	82	55	4.7	..	14

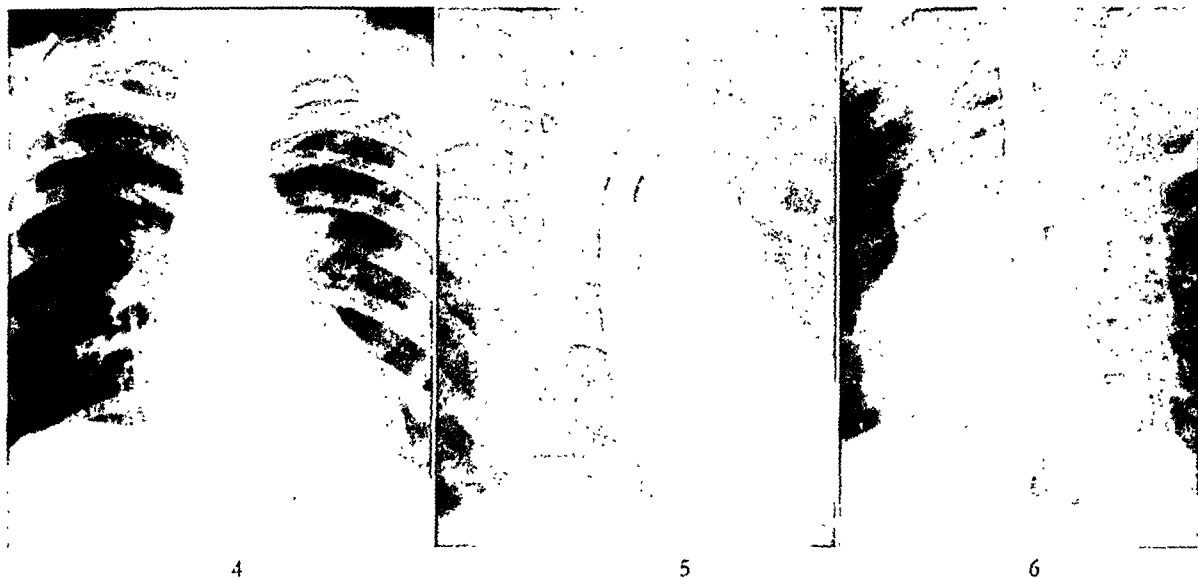


FIG. 4. Roentgenogram of the patient's chest in Case 1, postero-anterior projection.

FIG. 5. Roentgenogram of the patient's chest in Case 1, right anterior oblique projection. The esophagus is outlined with barium.

FIG. 6. Roentgenogram of the patient's chest in Case 1, left anterior oblique projection. The esophagus is outlined with barium.

the postero-anterior view there was a prominent rounded shadow which, however, showed very little pulsation; a slight concavity was present immediately below this shadow. In the right anterior oblique view there was some flattening in the region of the outflow area of the right ventricle while above this there was prominence of the pulmonary artery. In the left anterior oblique view moderate enlargement of the right ventricle was apparent. There was no increase in the vascular markings in the lung fields. The electrocardiogram showed slight right axis deviation.

CASE II. F. P., a twenty-two year old white male, was admitted to the chest service of Bellevue Hospital for thoracoplasty for right upper lobe tuberculosis of four years' known duration. Heart disease had been discovered at ten years of age in elementary school, but the only symptom was easy fatigability on exertion. Cyanosis had never been noted.

Physical examination showed a sternal depression, with considerable forward bulging of the chest close to the sternum. Examination of the lungs showed signs of a right upper lobe cavity. The second pulmonic sound was louder than the second aortic sound but not markedly accentuated. There was a long, loud, harsh, systolic murmur over the third and fourth left intercostal spaces, poorly transmitted to the axilla. It was audible in the second left inter-

space but was not so loud. A systolic thrill was palpable over the lower left sternal border. Fluoroscopic and x-ray examinations (Figs. 7, 8 and 9) showed an enlarged pulsating pulmonary artery and left main branch. The right pulmonary artery appeared small in size as did the aorta. No other vessels or heart chambers were abnormal in size. The electrocardiogram showed no axis deviation.

Six months previously angiocardigraphy had been performed at another hospital. This was reported to show enlargement of the main pulmonary artery and its left branch. The diameter of the ascending aorta was less than that of the pulmonary artery. The descending aorta was half the diameter of the ascending aorta and appeared hypoplastic. There was no evidence of abnormal shunts.

CASE III. S. S., a fifteen year old colored male who was admitted to Bellevue Hospital because of lobar pneumonia, had been told that he had had heart trouble since birth. He had no rheumatic history. His only cardiac complaint was mild dyspnea while playing basketball. Aside from the signs of pneumonia, the physical examination showed an audible but not accentuated pulmonic second sound. A systolic murmur was loudest over the mid-sternum but was transmitted along the clavicle and into the left interscapular region. It was accentuated during deep inspiration. Above



FIG. 7. Roentgenogram of the patient's chest in Case II, postero-anterior projection.

FIG. 8. Roentgenogram of the patient's chest in Case II, right anterior oblique projection.

FIG. 9. Roentgenogram of the patient's chest in Case II, left anterior oblique projection.

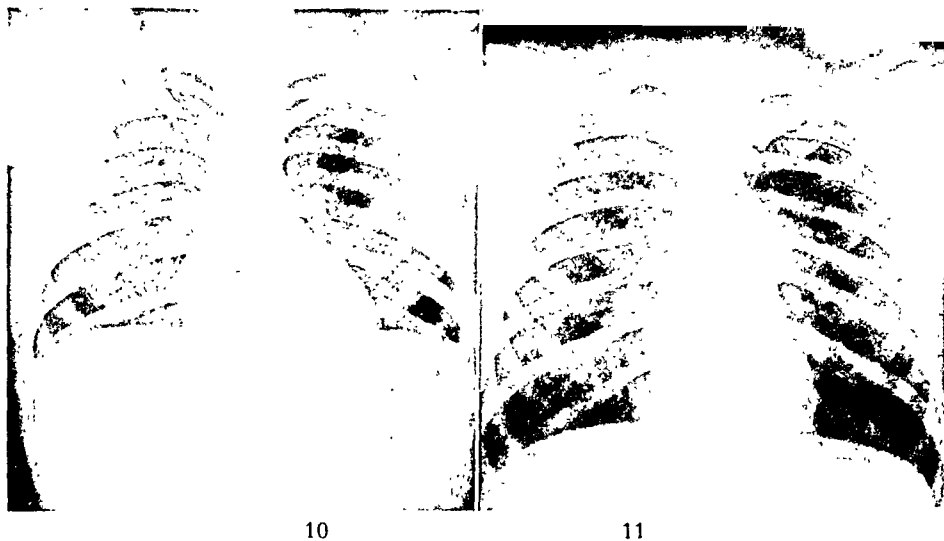


FIG. 10. Roentgenogram of the patient's chest in Case III; note the absence of enlargement of the pulmonary artery.

FIG. 11. Roentgenogram of the patient's chest in Case IV.

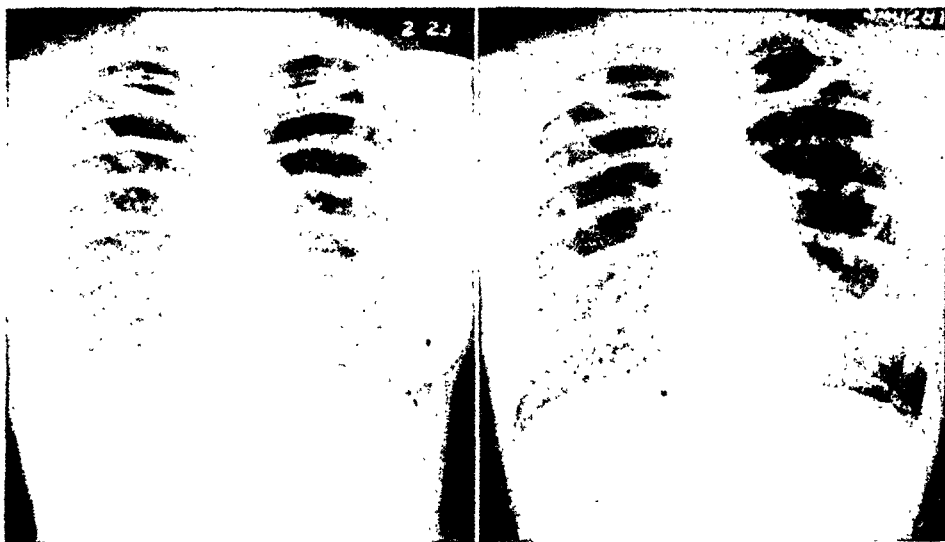
the right clavicle there was a systolic thrill. Fluoroscopy showed increased pulsations of the middle third of the left border of the heart and of the ascending aorta. There was questionable enlargement of the ventricles on x-ray examination. (Fig. 10.)

CASE IV. H. W., a marine aged nineteen, was referred to the Presbyterian Hospital for cardiac catheterization to rule out a patent ductus arteriosus. A heart murmur had been noted in infancy but he had been told he would "outgrow it." He had no complaints and his

lesion had first been noted in a routine chest x-ray. (Fig. 11.)

Physical examination of the heart was negative except for a systolic murmur and thrill in the pulmonic area. The murmur was transmitted to the neck and to the interscapular region. The pulmonic second sound was not accentuated. The electrocardiogram was normal.

The patient had previously been studied at another hospital where angiocardiology was reported to demonstrate a markedly dilated left pulmonary artery. The main pulmonary



12

FIG. 12. Roentgenogram of the patient's chest in Case v.

13

FIG. 13. Roentgenogram of the patient's chest in Case vi.

artery and right branch were of normal size. The cardiac chambers and aorta were normal in appearance.

CASE V. E. L., a white salesgirl aged seventeen, was referred to the Presbyterian Hospital for surgical correction of a patent ductus arteriosus. Her activities had been limited because of "heart trouble," but she herself had only minor subjective complaints of dyspnea on exertion and occasional mild pains in the region of the left breast. She was able to go to school and to work as a salesgirl. Physical examination showed a normal heart except for a loud blowing systolic murmur best heard in the pulmonic area, not well transmitted elsewhere. The pulmonic second sound was louder than the aortic second sound. The laboratory findings, including an electrocardiogram, were normal. Roentgenologic examination showed an enlargement in the region of the pulmonary artery. (Fig. 12.)

In spite of the evidence against the presence of a patent ductus arteriosus obtained by catheterization, exploration was carried out. It was one of the earliest cases of suspected congenital heart disease studied by catheterization, and the value of the method had not yet been fully established.

At operation the pulmonary artery was found to be much dilated, and a thrill could be felt which seemed to originate in the region of the pulmonary valve. The ligamentum arteriosum showed no patent lumen. Convalescence was uneventful, and the patient was symptom-free

and well when last seen nineteen months after the operation.

CASE VI. H. T., a white school girl aged fourteen, was referred to the Presbyterian Hospital because of an unusual cardiac silhouette discovered on routine x-ray examinations at school. A patent ductus arteriosus was suspected. She had no complaints. There was no history of cyanosis. Examination of the heart was normal except for a pulmonic systolic murmur which could be heard only after exercise. The pulmonic second sound was louder than the aortic second sound. The electrocardiogram was normal. X-ray showed an enlargement of the pulmonary artery. (Fig. 13.)

CASE VII. L. S., a thirteen year old white school girl, was referred to the Presbyterian Hospital with a possible case of patent ductus arteriosus. She had been well all her life, but on doctor's advice had refrained from games at the age of six. No reason was given for this restriction. Seven months before entry she noted slight exertional dyspnea, and after she was told by one doctor that she had rheumatic heart disease she complained of mild anterior chest pain. Immediately after this she began to have insomnia. These symptoms were completely relieved by reassurance. There was no history of cyanosis.

Physical examination showed an accentuated second sound in the pulmonic area and at the same point a systolic murmur and thrill. The



FIG. 14. Roentgenogram of the patient's chest in Case VII.

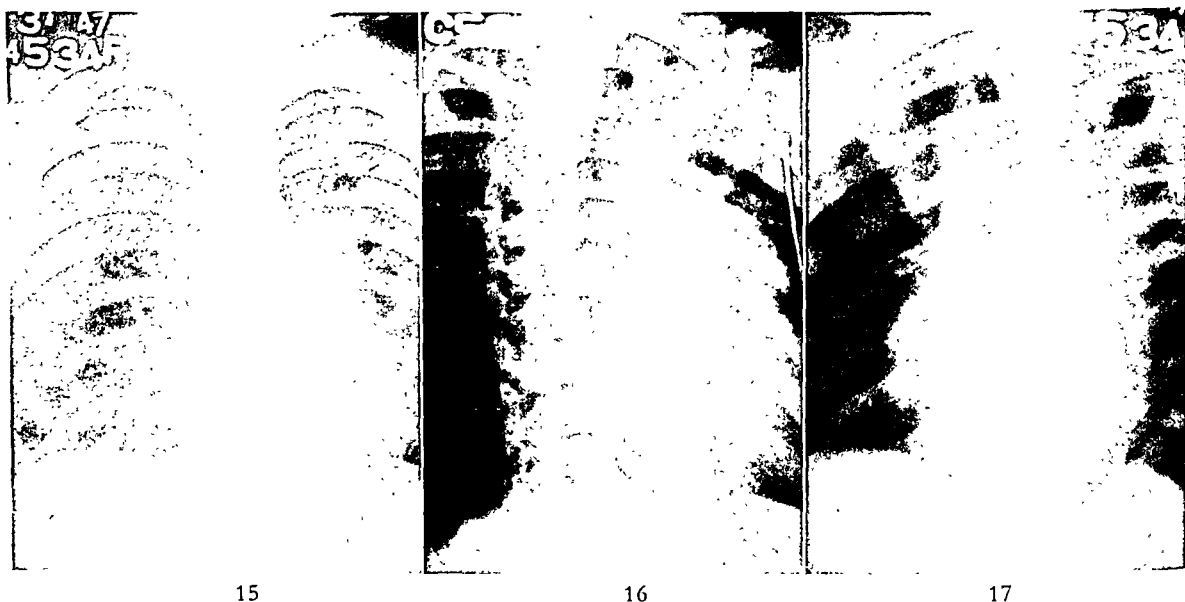
murmur was heard well all over the precordium and was transmitted to the vessels of the neck and faintly to the back. Fluoroscopy and x-ray examination showed an enlarged pulmonary artery with prominent pulsations. (Fig. 14.) The electrocardiogram was normal.

CASE VIII. J. P., a six year old girl, had been known since birth to have a heart murmur. She had developed normally but perhaps fatigued a little more easily than other children. Physical examination showed a funnel depression at the lower end of the sternum. No cyanosis or

clubbing was present and no dyspnea after moderately severe exercise. The heart was slightly enlarged to the left at the apex, with an increase in width to the left at the base easily demonstrated by percussion. A systolic thrill was felt in the pulmonic area and the pulmonic second sound was very slightly accentuated. There was a loud, coarse systolic murmur heard best in the second left interspace, and an early less loud, blowing decrescendo diastolic murmur heard best in the third left interspace. The blood pressure was 105/70 mm. Hg before exercise, 112/75 mm. Hg after exercise. Fluoroscopy and x-ray examination of the heart showed a striking enlargement of the pulmonary artery and its left main branch; there was no enlargement of the other pulmonary vessels or "hilar dance." The apex of the heart was rounded and slightly lifted. (Figs. 15, 16 and 17.) The electrocardiogram showed slight right axis deviation and right bundle branch block.

COMMENTS

Normally the right ventricle and pulmonary artery are in free communication throughout most of systole and therefore the systolic pressure is the same. In the patients herein reported there is a significant drop between the systolic pressure in the right ventricle and that in the pulmonary artery. This drop of pressure may be



FIGS. 15, 16 and 17. Roentgenograms of the patient's chest in Case VIII; postero-anterior projection (Fig. 15); right anterior oblique projection (Fig. 16); left anterior oblique projection (Fig. 17).

related either to an organic pulmonary stenosis or to a simple dilatation of the pulmonary artery. In the first instance the presence of a narrow outlet causes hypertension in the right ventricle. In the second instance pressure is dissipated as the result of an abnormal deformability of the pulmonary artery and of its main branches due to dilatation and the thinness of the wall and because the flow at the site of the dilatation becomes turbulent. The systolic pressure in the right ventricle obviously should not be increased.

These cases may therefore be divided into two groups on the basis of the systolic pressure in the right ventricle:

Group I consists of pulmonary stenosis and group II consists of idiopathic dilatation of the pulmonary artery.

A mechanism suggested by Chisholm³¹ may indicate that a stenosis of a particular type is present in simple dilatation of the pulmonary artery. He pointed out that the structures of the pulmonary orifice are easily stretched and when this orifice enlarges with dilatation of the pulmonary artery, the tissue most resistant to stretching is the free edge of the semilunar cusps. Then these free edges, instead of being closely applied to the arterial wall as they normally are during systole, may make three cords across the orifice and thus impede the flow of blood. This process, which he calls trigonoidation, Chisholm advances as the cause of a basal systolic murmur in patients with dilated pulmonary arteries. It seems possible that in addition to producing a murmur the taut edges of the leaflets might act to produce a slight degree of relative stenosis.

The grouping of these eight patients on the basis of pressure changes in the right ventricle corresponds to only one clinical sign. Three of the four patients in group I had normal pulmonic second sounds and in the fourth it was diminished in intensity. In group II the pulmonic second sound was accentuated in all four cases.

The results of the exercise are chiefly of interest in that they demonstrate the ability of the three patients tested to increase their

cardiac output. This is particularly striking in Case IV in which the cardiac output was tripled. This illustrates very well the difference between pure pulmonary stenosis and the tetralogy of Fallot. In the latter at rest there is a right to left shunt and a consequent diminution of flow through the pulmonary artery. As this shunt increases with exercise the deficit of pulmonary blood supply increases. Holman and Beck⁷⁰ have demonstrated experimentally that pulmonary arterial stenosis is well tolerated, causing less cardiac muscle hypertrophy than a large interventricular shunt. In the clinical case with intact septa the entire output of the right heart goes to the lungs and as long as the right ventricle is able to overcome the obstruction to outflow no functional impairment results.

SUMMARY

1. Sixty-eight cases of pure congenital pulmonary stenosis without abnormal shunts, the diagnosis established at autopsy, have been collected from the literature and the chief clinical and anatomic features are described.

2. Eight cases of pure congenital dilatation of the pulmonary artery have been selected from the literature of the last thirty years as being unequivocal examples of that lesion and a summary of the clinical and anatomic features is given.

3. Four additional examples of each of these lesions are reported.

4. Hemodynamic studies of these eight patients demonstrate the absence of abnormal shunts and the presence of a differential between the systolic pressure in the pulmonary artery and that in the right ventricle.

5. A division of these patients into two groups on the basis of the pressure in the right ventricle and the intensity of the pulmonic second sound is proposed.*

* Since this paper was submitted for publication, three cases of pure pulmonary stenosis diagnosed by means of cardiac catheterization have been reported. POLLACK, A. A., TAYLOR, B. E., ODEL, H. M. and BURCHELL, H. B. Pulmonary stenosis without septal defect. *Proc. Staff Meet., Mayo Clin.*, 23: 516, 1948.

REFERENCES

1. ABBOTT, M. E. Congenital heart disease. In Nelson's Loose Leaf Medicine. Vol. 4, p. 207. New York, 1932. Thomas Nelson & Sons.
2. ABBOTT, M. E. Atlas of Congenital Cardiac Disease. New York 1936. The American Heart Association.
3. ALEXANDER, A. A., KNIGHT, H. F. and WHITE, P. D. The auricular wave (P) of the electrocardiogram. Clinical observations with especial reference to pulmonic and mitral stenosis. *Arch. Int. Med.*, 36: 712, 1925.
4. ARNETT, J. H. and LONG, C. F. A case of congenital stenosis of the pulmonary valve with late onset of cyanosis. Death from carcinoma of the pancreas. *Am. J. M. Sc.*, 182: 212, 1931.
5. ARNHEIM, G. Ein Fall von angeborener Pulmonalstenose, sowie Bemerkungen über die Diagnose des offenen Ductus Botalli. *Berl. klin. Wchnschr.*, 42: 206, 1905.
6. ASCARELLI, A. Intorno a un caso di ectasia aneurismatica dell'arteria polmonale. *Policlinico sez. prat.*, 39: 679, 1932.
7. ASH, R., WOLMAN, I. J. and BROMER, R. S. The diagnosis of congenital cardiac defects in infancy. *Am. J. Dis. Child.*, 58: 8, 1939.
8. AUBERTIN, CHARLES. Rétrécissement congénital de l'artère pulmonaire et tuberculose pulmonaire. *Paris méd.*, 1: 413, 1935.
9. AUERBACH, O. and STEMMERMAN, M. G. Development of pulmonary tuberculosis in congenital heart disease. *Am. J. M. Sc.*, 207: 219, 1944.
10. BARIÉ, E. Le rétrécissement pré-artériel de l'artère pulmonaire. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 12: 579, 1895.
11. BAUER, D. DEF. and ASTBURY, E. C. Congenital cardiac disease. Bibliography of the 1000 cases analyzed in Maude Abbott's atlas. *Am. Heart J.*, 27: 688, 1944.
12. BENEDIKT, J. and BENEDIKT, E. Ein Fall von Insufficiencia valv. semilun. arteriae pulmonalis. *Wien. med. Wchnschr.*, 4: 548, 1854.
13. BERNARD, C. Quelques remarques sur les lésions valvulaires des cavités droites du cœur, à propos d'un cas de rétrécissement siégeant dans le ventricule droit. *Arch. gén. de Méd.*, 8: 161, 1856.
14. BISHOP, L. F., BISHOP, L. F. JR. and WALLACE, S. C. Pulmonary stenosis with bacterial endocarditis in an adult. *Am. Heart J.*, 5: 238, 1929.
15. BLACKFORD, L. M. and PARKER, F. P. Pulmonary stenosis with bundle branch block; report of case with sound tracings and semiserial studies of conduction bundle. *Arch. Int. Med.*, 67: 1107, 1941.
16. BONNAMOUR and DUMAREST. Sur un cas de rétrécissement pulmonaire congénital. *Lyon méd.*, 164: 182, 1940.
17. BOYD, L. J. and MCGAVACK, T. H. Aneurysm of the pulmonary artery. A review of the literature and report of two new cases. *Am. Heart J.*, 18: 562, 1939.
18. BRENNER, O. Pathology of the vessels of the pulmonary circulation. *Arch. Int. Med.*, 56: 211, 457, 724, 976, 1189, 1935.
19. BRET, JEAN. Le rétrécissement pulmonaire à évolution prolongée. (Étude clinique d'après 27 observations nouvelles.) Lyon thesis, 1936.
20. BROCK, R. C. Pulmonary valvulotomy for the relief of congenital pulmonary stenosis. Report of three cases. *Brit. M. J.*, 1121, 1948.
21. BROWN, J. W. Congenital Heart Disease. London, 1939. John Bale & Staples, Ltd.
22. BUDIN, P. Rétrécissement acquis de l'orifice pulmonaire; pas de phthisie pulmonaire. *Bull. Soc. Anat. Paris*, 8: 447, 1873.
23. BURKE, JOSEF. Angeborene Pulmonalstenose. *Zeitschr. f. Heilkunde, Abtheilung f. Interne Medicin*, 23: 209, 1902.
24. BURNET. Observations de maladies du cœur. *J. Univ. Hebd. de Méd. et de Chir.*, 1: 65, 1830.
25. CABRERA CALDERÍN, J. C. and LABOURDETTE SCULL, J. M. Un caso de endo-arteritis sub-aguda bacteriana en una estrechez pulmonar. *Bolet. Soc. cubana de pediat.*, 9: 457, 1937.
26. CARSWELL, ROBERT. Pathological Anatomy. London, 1838. Longman, Orme, Brown, Green and Longman.
27. CAUTLEY, EDMUND. Congenital pulmonary regurgitation (transposition of the spleen). *Brit. J. Child. Dis.*, 17: 187, 1920.
28. CAVINA, GIOVANNI. Stenosi sperimentale dell'arteria polmonare. *Arch. per le sc. med.*, 39: 6, 1915.
29. CEJKA. Drei Beobachtungen von Verwachsung des Herzbeutels. *Vierteljahrsschrift f. d. prak. Heilkunde, Praguer*, 46: 128, 1855.
30. CHIELIUS, M. J. Drei Beobachtungen organischer Herzerkrankheiten. *Heidelberger klin. Annalen*, 3: 412, 1827.
31. CHISHOLM, D. R. Trigonoidation of the semilunar valves and its relationship to certain basal systolic murmurs. *Am. Heart J.*, 13: 362, 1937.
32. CHRÉTIEN, E. Contribution à l'étude du rétrécissement pulmonaire préartériel acquis. *Rev. de méd.*, 13: 696, 1893.
33. CLARKE, J. J. A case of ulcerative endocarditis associated with stenosis of the conus arteriosus affecting chiefly the pulmonary valve, with ulceration of the main pulmonary artery. *Tr. Path. Soc. London*, 44: 29, 1893.
34. COSTA, A. Morfologie e patogenesi degli aneurismi dell'arteria polmonare. (Sopra un caso di voluminosi aneurismi multipli del tronco e dei grossi e medi rami, su base malformativa.) *Arch. di pat. e clin. med.*, 8: 257, 1929.
35. CRAIGIE. Notice of a case of cyanosis, or the blue disease, connected with mutual adhesion of the semilunar valves of the pulmonary artery. *Edinburgh M. & S. J.*, 60: 265, 1843.
36. CRUVEILHIER, JEAN. Anatomie Pathologique du Corps Humain. Paris, 1835-1842. J. B. Baillière.
37. CURRENS, J. H., KINNEY, T. D. and WHITE, P. D. Pulmonary stenosis with intact interventricular septum; report of eleven cases. *Am. Heart J.*, 30: 491, 1945.
38. D'AUNOY, RIGNEY and VON HAAM, EMMERICH. Aneurysm of the pulmonary artery with patent ductus arteriosus (Botallo's duct). *J. Path. & Bact.*, 38: 39, 1934.
39. DE NAVASQUEZ, S., FORBES, J. R. and HOLLING, H. E. Right ventricular hypertrophy of unknown origin: so-called pulmonary hypertension. *Brit. Heart J.*, 2: 177, 1940.

40. D'HEILLY. Des obliterations et rétrécissements congénitaux de l'artère pulmonaire. Paris thesis, 1864. Cited by Paul.⁹⁶
41. DITTRICH. Die wahre Herzstenose, erläutert durch einen Krankheitsfall. *Vierteljahrsschrift f. d. prak. heilkunde, Prague*, 21: 157, 1849.
42. DRESLER, K. Beitrag zur Diagnose der Persistenz des Ductus arteriosus Botalli. *Jahrb. f. Kinderh.*, 56: 705, 1902.
43. DRESLER, K. Nachtrag zur Diagnose der Persistenz des Ductus arteriosus Botalli. *Jahrb. f. Kinderh.*, 60: 571, 1904.
44. DUGUET. Rétrécissement de l'orifice artériel pulmonaire, non suivi de phthisie, chez une rhumatisante, hémiplegie faciale, néphrite parenchymateuse mortelle. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 19: 5, 1882.
45. DUGUET and LANDOUZY. Note sur un cas de rétrécissement acquis de l'artère pulmonaire chez un malade mort de tuberculose généralisée. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 15: 164, 1878.
46. DUMAS and PIPARD. Rétrécissement congénital de l'artère pulmonaire. *Lyon méd.*, 138: 49, 1926.
47. DUREY-COMTE, PIERRE. Contribution à l'étude du rétrécissement congénital de l'artère pulmonaire. Paris thesis, 1887.
48. EAKIN, W. W. and ABBOTT, M. E. Stenosis of the pulmonary conus at the lower bulbar orifice (conus a separate chamber) and closed interventricular septum with two illustrative cases. *Am. J. M. Sc.*, 186: 860, 1933.
49. EAST T. Pulmonary hypertension. *Brit. Heart J.*, 2: 189, 1940.
50. ELLIOTSON. The Recent Improvements in the Art of Distinguishing the Various Diseases of the Heart. London, 1830. Longman & Co.
51. ESCALLE, J. E. J. Etude critique du diagnostic clinique du rétrécissement congénital isolé de l'artère pulmonaire. Paris thesis, 1942.
52. ESSER, A. Seltene Formen von Aneurysmen. *Ztschr. f. Kreislaufforsch.*, 24: 737, 1932.
53. FALLOT. Quoted in *London M. & S. J.*, 5: 61, 1834.
54. FLINT, AUSTIN, SR. A specimen of stenosis of the pulmonary artery. *M. News*, 44: 287, 1884.
55. FREED, A. N. and BUDNITZ, J. Pure congenital pulmonary stenosis. *Am. Heart J.*, 31: 369, 1946.
56. GARRISON, R. E. and FELDT, R. H. Congenital pulmonary stenosis with closed cardiac septa. *Am. Heart J.*, 24: 685, 1942.
57. GENERSICH, ANTAL. Stenosis ostii arteriosi dextri. Aneurysma trunci arteriae pulmonalis. *Orvosi hetil.*, 51: 614, 1907.
58. GIBSON, S. and CLIFTON, W. M. Congenital heart disease. *Am. J. Dis. Child.*, 55: 761, 1938.
59. GOLD, M. M. A. Congenital dilatation of pulmonary arterial tree; relation to Ayerza's disease and primary pulmonary arteriosclerosis. *Arch. Int. Med.*, 78: 197, 1946.
60. GRENET, H. and FRANCOIS-JOLY, J. Rétrécissement de l'artère pulmonaire et tuberculose. *Arch. de méd. d. enf.*, 39: 789, 1936.
61. GRISHMAN, A., STEINBERG, M. F. and OPPENHEIMER, B. S. The clinical diagnosis of idiopathic dilatation of the pulmonary artery. *J. Mt. Sinai Hosp.*, 10: 142, 1943-1944.
62. GRISHMAN, A., STEINBERG, M. F. and SUSSMAN, M. L. Congenital aortic and sub-aortic stenosis with associated anomalies of the aorta. *M. Clin. North America*, 31: 543, 1947.
63. GUINSBOURG, SARAH. Sur le frequence de la localization dans la troisième espace intercostal gauche du souffle systolique du rétrécissement pulmonaire. Paris thesis, 1914.
64. HAVAGE. Rétrécissement de l'artère pulmonaire et épanchement pericardique abondant. Absence de tubercules pulmonaires. Foie cardiaque. Néphrite mixte. *Bull. Soc. Anat. Paris*, 4: 562, 1879.
65. HEBB, R. G. Stenosis of pulmonary artery. Congenital heart disease. *Tr. Path. Soc. London*, 41: 57, 1890.
66. HENSCHEN, S. E. Das aneurysma arteriae pulmonalis. *Samml. Klin. Vort., Volkmann*, 422-33, *Innere Medizin N. F.*, 126-127, 1906.
67. HERTZ, THEODOR. Ein Fall von angeborener Pulmonalstenose ohne andere Dysplasien und Aplasien, mit positivem Deneke'schen Zeichen. *Ztschr. f. Kreislaufforsch.*, 24: 446, 1932.
68. HERXHEIMER, GOTTHOLD. In SCHWALBE, ERNST. Die Morphologie der Missbildungen des Menschen und der Tiere. Vol. 3, P. 401. Jena, 1910. Gustav Fischer.
69. HOWARTH, SHEILA, McMICHAEL, J. and SHARPEY-SCHAFER, E. P. Cardiac catheterization in cases of patent interauricular septum, primary pulmonary hypertension, Fallot's tetralogy, and pulmonary stenosis. *Brit. Heart J.*, 9: 292, 1947.
70. HOLMAN, E. and BECK, C. S. Physiological response of circulatory system to experimental alterations; effect of aortic and pulmonic stenoses. *J. Clin. Investigation*, 3: 283, 1926.
71. JENNES, S. W. Diffuse aneurysmal dilatation of the pulmonary artery and both of its branches. *Bull. Johns Hopkins Hosp.*, 59: 133, 1936.
72. JOSSERAND. Rétrécissement de l'artère pulmonaire. *Lyon méd.*, 106: 674, 1906.
73. KEITH, ARTHUR. The Hunterian Lectures on malformations of the heart. *Lancet*, 2: 359, 433, 519, 1909.
74. KOEHLER, CURT. Beiträge zur Casuistik der Stenose des Ostium pulmonale. Halle thesis, 1894.
75. KOURILSKY, RAOUL, GUÉDÉ, MARCEL and REGAUD, JEAN. Les dilatations congénitales de l'artère pulmonaire. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 56: 772, 1941.
76. KOURILSKY, RAOUL, KOURILSKY, SIMONE, MARCHAL, MAURICE and GOUBERT, J. L. Sur le frequence relative des dilatations congénitales du tronc de l'artère pulmonaire. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 58: 246, 1942.
77. KOURILSKY, RAOUL, REGAUD, JEAN and DUGRENOT, HENRI. Erythémie chez une malade atteinte d'une dilatation de l'artère pulmonaire. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 56: 762, 1941.
78. KOURILSKY, R., REGAUD, J. and RÉMOND, S. Verification anatomique d'un cas de dilatation congénitale du tronc et des branches de l'artère pulmonaire, compliqué de stenose mitrale et d'atherome pulmonaire. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 58: 245, 1942.
79. LAFITTE, A. Rétrécissement infundibulaire de l'artère pulmonaire d'origine congénitale. Obliteration incomplète du trou de Botal. Absence

- de cyanose. Endocardite végétante au niveau du rétrécissement. *Bull. et mém. Soc. Anat. de Paris*, 6: 13, 1892.
80. LAUBRY, CHARLES and PEZZI, C. Traité des maladies congénitales du cœur. Paris, 1921. J. B. Baillière.
 81. LAUBRY, CHARLES, ROUTIER, DANIEL, WALSER, J. and DOUMER, ED. Nouveau Traité de Pathologie Interne. III. Maladies du cœur et des vaisseaux. Paris, 1930. Gaston Doin & Cie.
 82. LAUBRY, CHARLES. Discussion of Kourilsky.⁷⁷ *Bull. et mém. Soc. méd. d. hôp. de Paris*, 56: 770, 1941.
 83. LECLERC and BARJON. Rétrécissement pulmonaire congénital. *Bull. Soc. méd. des Hôp. de Lyon*, 2: 463, 1903. Cited by Escalle⁵¹ and Guinsbourg.⁶³
 84. LEECH, C. B. Congenital heart disease. Clinical analysis of seventy-five cases from the Johns Hopkins Hospital. *J. Pediat.*, 7: 802, 1935.
 85. LETOUSEY. Rétrécissement de l'orifice de l'artère pulmonaire. *Bull. Soc. Anat. Paris*, 2: 472, 1877.
 86. LOWANCE, M. I., JONES, E. C., MATTHEWS, W. B. and DUNSTAN, E. M. Congenital pulmonary stenosis. *Am. Heart J.*, 35: 820, 1948.
 87. MAYER, M. Über einen Fall von Stenosierung der pulmonal Arterie in Folge von acuter Endocarditis der semilunar Klappen. *Deutsches Arch. f. klin. Med.*, 24: 435, 1879.
 88. MEYNET, P. Rétrécissement de l'orifice de l'artère pulmonaire consecutif à une endocardite valvulaire: phthisie pulmonaire; mort. *Gaz. méd. de Lyon*, 19: 538, 1867.
 89. NORMAN, H. B. Malformation of the pulmonary valves. *Brit. M. J.*, 2: 960, 1878.
 90. NORRIS, R. F. Primary pulmonary arteriosclerosis. Report of a case with marked calcification of the pulmonary arteries. *Bull. Johns Hopkins Hosp.*, 59: 143, 1936.
 91. OGLE, J. W. Abnormal condition of the valve at the root of the pulmonary artery, with consequent hypertrophy of the parietes of the right ventricle of the heart. *Tr. Path. Soc. London*, 5: 69, 1854.
 92. OPPENHEIMER, B. S. Idiopathic dilatation of pulmonary artery. *Tr. A. Am. Physicians*, 48: 290, 1933.
 93. ORMEROD, J. A. Disease of pulmonary valve. *Tr. Path. Soc. London*, 44: 30, 1893.
 94. PATIÑO MAYER, C. Endoarteritis y valvulitis ulcerovegetantes, en una estenosis congenita de la pulmonar. Infartos septicos multiples en ambos pulmones. *Semana méd.*, 2: 277, 1936.
 95. PAUL, CONSTANTIN. Du rétrécissement de l'artère pulmonaire contracté après la naissance. De ses symptômes et de ses complications. *Gaz. d. hôp. Paris*, 44: 202, 1871.
 96. PAUL, CONSTANTIN. Diagnostic et traitement des maladies du cœur. 2nd ed. Paris, 1887. Asselin and Houzeau.
 97. PEACOCK, T. B. Contraction of the orifice of the pulmonary artery from fusion of the valves. *Tr. Path. Soc. London*, 10: 107, 1859.
 98. PEACOCK, T. B. On Malformations of the Human Heart, etc. 2nd ed. London, 1866. J. C. A. Churchill, Ltd.
 99. PEACOCK, T. B. Case of stenosis of the pulmonary artery from disease of the valves, probably of congenital origin. *Tr. Path. Soc. London*, 30: 258, 1879.
 100. PHILOUZE. Dilatation considérable de l'oreillette droite du cœur; ossification de l'orifice auriculo-ventriculaire droit; ossification et rétrécissement considérable de l'orifice de l'artère pulmonaire, dilatation enorme de cette artère; hypertrophie du ventricule droit, etc. *Bull. Soc. Anat. Paris*, 1: 158, 1826.
 101. POTAIN and RENDU. Cœur (pathologie). Dechambre's Dictionnaire Encyclopedique des Sciences Médicales. 18: 619, 1876.
 102. RINSEMA, TH. Ein Fall von acquirirter Stenose des Ostium pulmonale. *Deutsches Arch. f. klin. Med.*, 34: 216, 1884.
 103. ROESLER, H. and KISS, A. Beiträge zur Lehre von den angeborenen Herzfehlern. VII. Elektrokardiographische Untersuchungen an 100 Fällen. *Wien. Arch. f. Inn. Med.*, 21: 271, 1931.
 104. ROSENTHAL, JOHANNES. Beitrag zur Casuistik der erworbenen Stenose der Pulmonalarterie durch Verwachsung der Klappensegel. Freiburg thesis, 1896.
 105. ROUTIER, D. Book review. ESCALLE, J. E. Étude critique du diagnostic clinique de rétrécissement congénital isolé de l'artère pulmonaire. Paris thesis, 1942. *Arch. d. mal. du cœur*, 36: 24, 1943.
 106. ROUTIER, D. and ESCALLE, J. E. A propos du diagnostic clinique du rétrécissement pulmonaire. *Arch. d. mal. du cœur*, 36: 59, 1943.
 107. ROUTIER, D. and ESCALLE, J. E. A propos des signes d'auscultation du rétrécissement pulmonaire. *Arch. d. mal. du cœur*, 38: 284, 1945.
 108. SCHNITKER, M. A. The Electrocardiogram in Congenital Cardiac Disease. Cambridge, 1940. Harvard University Press.
 109. SCOTT, R. B. Aneurysm of the pulmonary artery with report of a case. *Lancet*, 1: 567, 1934.
 110. SOLOMON, RAYMOND. Du rétrécissement pulmonaire acquis. Paris thesis, 1872.
 111. STÖLKER, CARL. Beiträge zur Pathologie der angeborenen Stenose der Arteria pulmonalis. *Schweiz. Ztschr. f. Heilkunde*, 3: 3, 4, 1864.
 112. STÖLKER, CARL. Ueber angeborene Stenose der Arteria pulmonalis. Bern, 1864. Haller.
 113. SUSSMAN, M. L., GRISHMAN, A. and STEINBERG, M. F. Newer concepts in the diagnosis of congenital heart disease. *Am. J. Dis. Child.*, 65: 922, 1942.
 114. SUTHERLAND, G. A. Symptoms and signs in chronic heart disease. *Brit. J. Child. Dis.*, 19: 1, 1922.
 115. SUTHERLAND, G. A. A case of congenital aneurysm of the pulmonary artery. *Brit. J. Child. Dis.*, 20: 27, 1923.
 116. TARUFFI, CESARE. Caso di stenosi acquisita dell'arteria pulmonare. *Bull. d. sc. med.*, 19: 225, 1875.
 117. TAUSSIG, H. B. Congenital Malformations of the Heart. New York, 1947. The Commonwealth Fund.
 118. TIEDEMANN, FRIEDRICH. Von der Verengung und Schliessung der Pulsadern in Krankheiten. Heidelberg and Leipzig, 1843. Karl Groos.
 119. WHITLEY, G. Cases of disease of the pulmonary artery and its valves. *Guy's Hosp. Rep.*, 3: 252, 1857.

Aureomycin in the Treatment of Primary Atypical Pneumonia*

YALE KNEELAND, JR., M.D., HARRY M. ROSE, M.D. and COUNT DILLON GIBSON, M.D.

New York, New York

AUREOMYCIN is a new antibiotic derived from a *Streptomyces* by Duggar of Lederle Laboratories.¹ Preliminary studies² indicated that it was effective not only against a wide bacterial spectrum, both gram-positive and gram-negative, but also against rickettsial infections in experimental animals.³ In addition it was shown to exert a curative action on two experimental virus infections in mice, lymphogranuloma venereum and psittacosis. Moreover, acute and chronic toxicity studies in animals indicated that it would in all probability be suitable for administration to human beings.

Since these early studies a few reports have appeared of its clinical use in the treatment of infections in man. It appears to be highly effective in all types of rickettsial disease thus far studied⁴ and also in lymphogranuloma venereum.⁵ A few citations of its use in bacterial infections have also appeared.⁴ To date no important toxic side effects have been described.

We propose to report our experiences with this agent in the treatment of primary atypical ("virus") pneumonia. Atypical pneumonia cannot be differentiated on purely clinical grounds from Q-fever or from human infection with the psittacosis-ornithosis group of viruses. Q-fever was known to be susceptible to aureomycin and there was reason to suppose from experimental studies³ that psittacosis also would be susceptible. Because of its known antiviral activity in these infections, aureomycin seemed worth a trial in primary atypical

pneumonia. Therefore, in July, 1948, when one of us was called to see an extremely ill patient who presented the clinical features of atypical pneumonia, treatment with aureomycin was instituted. A small supply of aureomycin had been made available to us by Dr. Herald Cox of the Lederle Laboratories.

Results in this patient, to be presented below, seemed sufficiently encouraging to warrant further trial. It is obvious that in treating a disease like atypical pneumonia, which is so variable and unpredictable in its course, conclusions must be drawn with the utmost caution. Nevertheless, as case has succeeded case the impression has deepened that following the administration of aureomycin a modification in the clinical severity of the disease takes place with regularity. For this reason it seems justified to publish the data on our first ten cases of atypical pneumonia treated with aureomycin in the hope that they will stimulate other studies along this line.

SELECTION OF CASES

The criteria we have established as to the selection of cases for treatment are as follows: (1) The patient must present the familiar clinical features of cough, fever, pneumonitis, normal leukocyte count, normal bacterial flora of sputum, etc., (2) the disease must have been unaffected by penicillin in full doses for at least forty-eight hours and (3) the patient must be getting worse at the time treatment is instituted.

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y.



FIG. 1. Case 1, chest x-ray taken on July 22nd, the day aureomycin treatment was started. Fairly extensive patchy infiltration of the right lung is evident.

DOSAGE OF DRUG AND METHOD OF ADMINISTRATION

Aureomycin hydrochloride may be injected parenterally by various routes but a wholly satisfactory vehicle has not yet been developed. The crystalline powder may be taken orally in capsules. When given in sufficient dosage by mouth, satisfactory blood levels are obtained and these are ordinarily maintained for at least six hours. The dosage we have employed has been somewhat varied. We have usually started treatment at a level of 4 Gm. daily in six-hourly divided doses, and then reduced this gradually in the succeeding days. Of late we have given an initial dose of 1.5 Gm., followed by 1.0 Gm. every six hours. In general, we have maintained the drug until the temperature has been down several days and the patient is substantially improved.

SIDE EFFECTS

Two of the ten patients developed nausea which seemed clearly related to the aureomycin. Vomiting often occurred an hour to an hour and a half after a dose in these two patients. It was not believed that this interfered materially with absorption. One patient presented anemia during convales-

cence. None of the other patients showed any serious untoward effects.

CASE REPORTS

CASE 1. (Patient of Dr. C. D. Dunham). A forty-seven-year-old white woman entered the hospital on July 17, 1948, with a five-day history of chilliness, malaise, cough, fever, pain in the chest, headache and hoarseness. She gave no history of exposure to infectious disease, animals or possible insect vectors.

On admission she appeared acutely ill, but apart from a reddened pharynx the general physical examination was not remarkable. As shown in the accompanying graph the temperature was only 99.8°F. but rose promptly to 102°F. Pulse rate at this time was 96 and in general tended to be somewhat low in proportion to the fever; respirations were 22. Chest x-ray was negative; the white blood count was 8,650 with 64 per cent polymorphonuclears; urine was negative. Sputum was negative for acid-fast organisms and no significant pathogens could be cultivated.

For the next twenty-four hours the fever remained fairly constant at this level but in the early hours of July 19th, following a chill, the temperature rose to 104°F. At this time she appeared worse; there was severe paroxysmal cough, mostly unproductive, together with more malaise, weakness and headache. The leukocyte count at this time was essentially unchanged, blood culture was negative, and a repeat x-ray was interpreted as showing possibly a minimal pneumonitis at the right base. Her temperature fell on salicylates during the day but rose again and reached 105°F. on July 21st. During the first four days in the hospital she was treated with intramuscular penicillin, 600,000 units a day.

On July 22nd her condition appeared more serious. During the night she had been disoriented. She was prostrated and the cough was intermittently very severe. She appeared dyspneic and crepitant rales were noted over the right lower lobe. As shown in Figure 1, an x-ray now revealed a fairly extensive patchy pneumonitis on the right. The decision to treat with aureomycin was made in the afternoon and the first dose of 1.0 Gm. given at 5:00 P.M.

As indicated in Figure 2 the temperature fell during the next day, rose during the night of the 23rd to 103°F. and then fell again on the morning of the 24th to essentially normal levels.

With the exception of a minor elevation to 100.6°F. that afternoon it remained normal thereafter.

It was noted that on the day following the start of treatment the patient appeared somewhat stronger and better generally. By July 24th

developed signs of an upper respiratory tract infection with nasal congestion and malaise. About thirty-six hours before admission a non-productive cough commenced, together with headache and a feeling of feverishness. Not long thereafter she had a shaking chill with a rise in

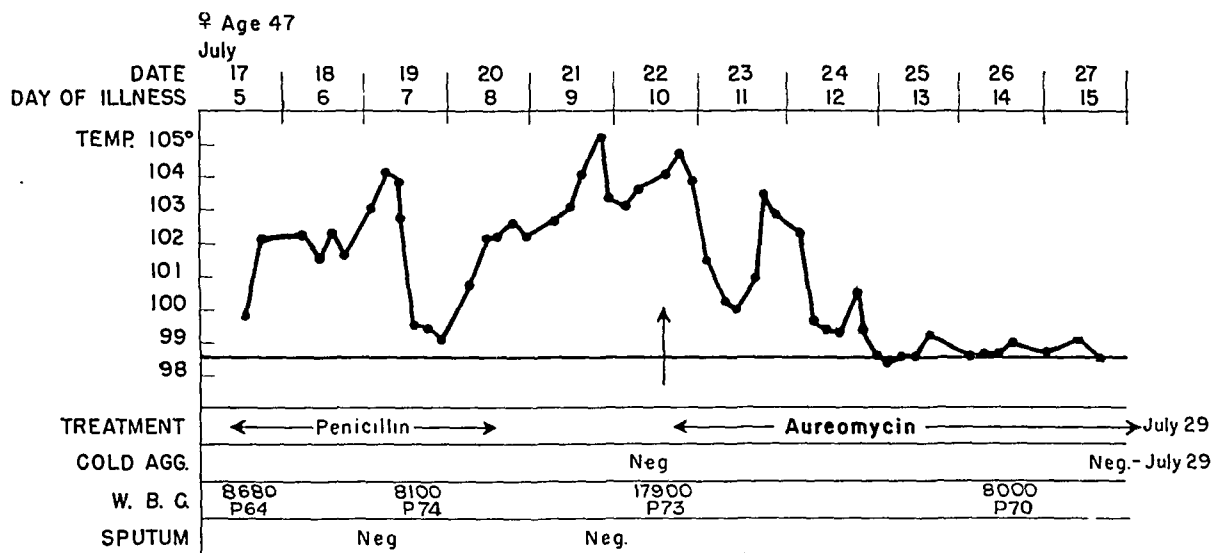


FIG. 2. Chart of Case 1.

this improvement was striking. The headache had disappeared, cough was less distressing and there was considerable increase in strength and sense of well being. Convalescence thereafter was uneventful. Treatment with 4 Gm. daily of aureomycin was maintained for a total of seven days. X-ray (Fig. 3) on July 27th showed almost complete clearing of the pneumonitis.

Serum specimens obtained at intervals during the acute illness and convalescence and tested for cold agglutinins were all negative. Complement-fixation tests for Q-fever and psittacosis were inconclusive. Thus we had no serologic clue to the etiology of this patient's disease. (Serologic tests for brucellosis, and the Weil-Felix and Widal tests were also negative.) Nevertheless we believed that the most probable diagnosis was primary atypical pneumonia of the familiar type.

The case was a rather severe one and all observers believed that aureomycin had an effect on its course, an effect, incidentally, similar in character to that described in Q-fever. The case has been reported in some detail because it was responsible for our subsequent trials of the antibiotic.

CASE II. The patient was a twenty-four year old student nurse who entered Harkness Pavilion on August 2, 1948. Three days earlier she had

oral temperature to 102°F. At the time of admission to the hospital she was acutely ill with a severe paroxysmal cough and a temperature of 101.8°F.

The physical examination revealed numerous moist rales over the base of the right lung posteriorly, and the chest x-ray showed mottled shadows in the region of the right lower lobe. The leukocyte count was 8,400 with a normal differential. No sputum could be obtained for bacteriologic examination but the throat culture was negative for respiratory pathogens.

During the next three days the patient received penicillin, one million units every twenty-four hours. Despite this treatment the temperature mounted progressively to 103°F., the cough continued unabated, and the physical signs over the right lower lobe became more pronounced. Penicillin was therefore discontinued and aureomycin was started on the fourth hospital day in a dose of 1.0 Gm. every eight hours given by mouth. Over the next forty-eight hours the temperature fell to normal, the cough virtually ceased and the patient noted a marked increase in her sense of well being. By the end of the third day on aureomycin all symptoms had disappeared with the exception of a slight residual cough. At this time the supply of the drug became exhausted and treatment therefore had

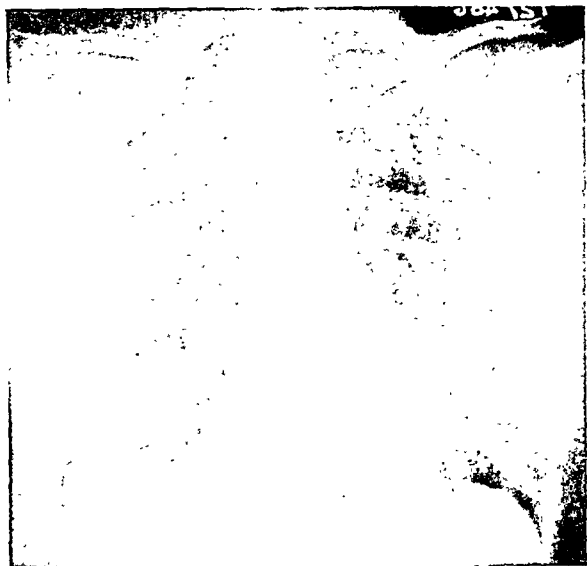


FIG. 3. Case 1. x-ray taken on July 27th, five days later. A remarkable degree of clearing has taken place.

to be stopped. Twenty-four hours later the temperature rose again to 100.2°F . and continued to fluctuate between 99° and 100°F . for the following week. Cough recurred and there was evidence by x-ray of extension of pulmonary involvement. No further treatment was given and the illness finally subsided uneventfully after about ten days. The cold agglutinin test was negative on admission, August 2nd, but was positive in a serum dilution of 1:64 on August 21st.

The character of the illness, the failure to respond to penicillin and the development of cold agglutinins indicate that the patient probably suffered from primary atypical pneumonia. The administration of aureomycin was followed by a prompt defervescence of clinical signs and symptoms suggesting a specific therapeutic response to the drug. The fact that the disease relapsed soon after the premature cessation of treatment supports this possibility.

CASE III. The patient was a fourteen year old schoolboy who was attending a summer camp. On about July 15, 1948, he developed an acute pharyngitis with fever and a persistent hacking cough. The pharyngitis rapidly subsided but the fever and cough continued, and he was confined to the camp infirmary for two weeks with an intermittent temperature ranging between 100° and 102°F . By the end of that time, however, all symptoms had subsided and he was discharged from the infirmary on July 30th apparently recovered, but still running an afternoon temperature of 99° to 99.6°F .

One week later, on August 6th, he again became acutely ill and his temperature rose to 102°F . The following day he began to have a productive cough and complained of pain in the chest. On August 8th he was admitted to the hospital in Sharon, Connecticut, under the care of Dr. Graham B. Blaine, to whom we are indebted for permission to report the case. On entry to the hospital an x-ray of the chest showed patchy pneumonic involvement of the right upper and middle lobes. The leukocyte count was 9,000 with a normal differential. The blood was negative for cold agglutinins. Culture of the sputum revealed no respiratory pathogens. During the next four days, on treatment with penicillin and sulfadiazine, the cough decreased, the temperature fell to normal and on August 12th the x-ray showed marked clearing. On the following day, however, the temperature again spiked to 103°F ., cough became more severe and chest pain returned. X-rays showed an extensive area of new pulmonary involvement in the region of the right lower lobe. Using doses of 0.3 Gm. every eight hours by mouth, treatment with aureomycin was begun on August 15th. Thirty-six hours later the temperature was normal, the cough and chest pain had ceased and the patient appeared much improved. Aureomycin was continued for an additional five days and recovery was uneventful. Another x-ray of the chest taken four days after the beginning of treatment with aureomycin showed almost complete resolution of the pneumonic process. A specimen of blood obtained during convalescence again was negative for cold agglutinins.

This patient had a relapsing febrile illness with a migratory type of pneumonitis, negative bacteriologic findings and absence of leukocytosis. Treatment with penicillin and sulfadiazine was apparently ineffective but the administration of aureomycin was followed by prompt defervescence of the disease. The diagnosis of primary atypical pneumonia seems fairly well established on clinical grounds, and it is known that cold agglutinins do not develop in about 25 per cent of cases. In addition, complement fixation tests for psittacosis and Q-fever were negative with both acute and convalescent phase blood specimens.

CASE IV. The patient was a thirty-eight year old colored female who entered the Presbyterian Hospital on August 30, 1948. Four days before admission she developed a hacking cough with

whitish, mucoid sputum. The cough became progressively worse and was accompanied by malaise, headache and a sensation of fever. On admission the temperature was 104.2°F. and the patient appeared acutely ill with a severe hacking cough productive of frothy, pinkish sputum.

The physical examination was essentially negative except for numerous moist rales over the right upper lobe. The white count was 10,900, with 84 per cent polymorphonuclears. The sputum culture was negative for significant pathogens. The blood culture was sterile. Penicillin was given for the first two days in a dose of 100,000 units every three hours without any apparent effect upon the course of the illness. For the first thirty-six hours the temperature ranged between 102° and 104.4°F. By the end of the second day the temperature had fallen to 101°F. but the patient still appeared ill, the cough was severe, and there were now signs of consolidation over the right upper lobe. Aureomycin was then started in a dose of 1 Gm. every eight hours. Eight hours after the first dose of aureomycin the patient appeared much better, the temperature had fallen to normal and the cough was less.

This improvement continued throughout the succeeding day. It appeared that this clinical response had occurred too rapidly for it to be attributable directly to an effect of the aureomycin and, therefore, with the patient apparently recovering spontaneously, the drug was discontinued after three doses had been given. However, on the following day the patient's temperature rose again to 100.6°F. and continued to fluctuate between 99° and 102°F. for the next seven days. During this period there was gradual improvement in symptoms and a decrease in extent of pulmonary involvement by physical and x-ray examination. The cold agglutinins, which had been negative on admission, rose to 1:256 nine days later. In retrospect it appears probable that the rapid improvement of the patient following the administration of aureomycin was actually due to the drug, especially since the initial therapeutic response was succeeded by a relapse of the disease soon after treatment was discontinued. The clinical pattern is similar to that of Case II in whom therapy was also stopped too soon.

CASE V. (Ward patient, Presbyterian Hospital.) A twenty-seven year old Puerto Rican male was admitted to the hospital on September

26th after thirty-six hours of chilly sensations, non-productive cough and aching pains. On entry his temperature was 103.4°F. and he appeared acutely ill. Apart from this, general physical examination was negative. However, the x-ray on admission showed some patchy pneumonitis in the left mid-lung area. His white count was 11,500 with 74 per cent polymorphonuclears. He was started on intramuscular penicillin, 100,000 units every three hours. The initial sputum was injected into a mouse and a Type XI pneumococcus grew out next day. However, a second specimen two days later was negative for pneumococci.

After forty-eight hours on large doses of penicillin he was worse and the temperature had risen to 105°F. X-ray showed some increase in the pneumonitis. At this time the penicillin was stopped and he was put on aureomycin. His fever declined by fairly rapid lysis, the temperature reaching and remaining normal forty-eight hours after commencement of therapy. (Fig. 4.) Within twenty-four hours, before the temperature was normal, there was a very striking subjective improvement, the patient stating he felt "like a brand new Buick." Cold-agglutinins were negative on September 27th and 30th. On October 7th they had risen to a titer of 1:1024.

This was a young man with an illness of short duration at the time of treatment. Following aureomycin he made a very rapid recovery. There had been no clinical response to forty-eight hours of penicillin therapy. The appearance of cold agglutinins in very high titer leaves no doubt as to the diagnosis.

CASE VI. (Patient of Capt. Berté, Fort Totten General Hospital.) The patient was a twenty year old soldier who entered the hospital on September 27th with a two-day history of sore throat, tight cough and feverishness. On admission his temperature was 102°F., pulse rate 120. The temperature curve is illustrated by the accompanying graph (Fig. 5) and during the course of his illness his pulse rate corresponded closely to the height of his fever. He was acutely ill with paroxysmal cough, and rales were noted at both the bases. The admission leukocyte count was 9,300; polymorphonuclears, 72 per cent. Sputum culture showed no pathogens. Urine was negative. X-ray showed a patchy pneumonitis, mainly in the right mid-lung area.

He was started on intramuscular penicillin, 50,000 units every three hours. As can be seen from Figure 5, this treatment had no apparent effect on the fever. By October 1st he was distinctly worse; his cough was almost incessant, more rales were audible over both bases and

was some evidence of "Mediterranean Trait" (i.e., racial origin, palpable spleen tip, target cells, and decreased erythrocyte fragility). Wright et al.⁵ described anemia occurring in some of their lymphogranuloma venereum patients treated with aureomycin parenterally

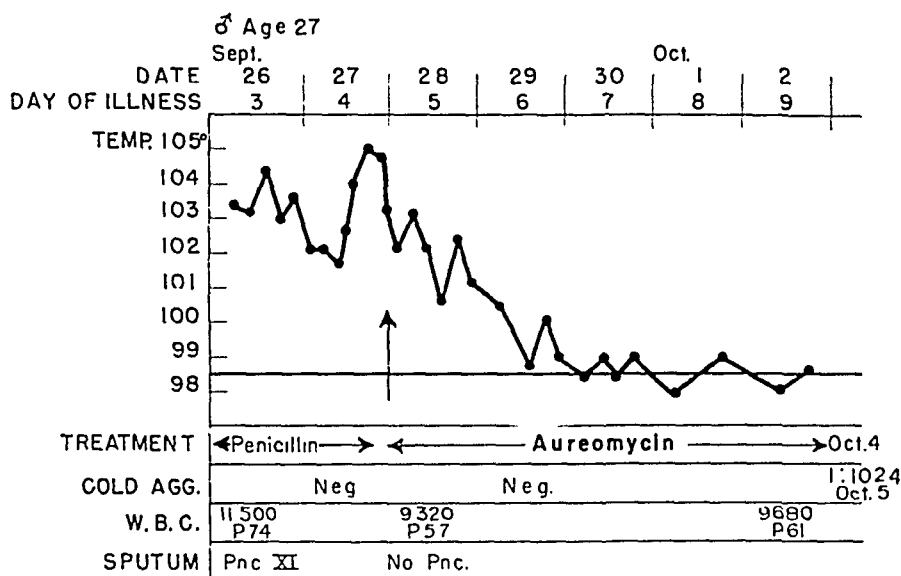


FIG. 4. Chart of Case v.

x-ray showed extension of the pneumonitis to the left lower lobe, with more involvement also on the right. That evening his temperature rose to its highest point, 103°F., and he was started on aureomycin with an initial dose of 1.5 Gm., 1.0 Gm. every six hours to follow on the ensuing day. As can be seen from Figure 5 his temperature fell, reaching and remaining normal forty-eight hours after therapy was instituted. At this time, although he still had considerable cough and many rales were still audible, there was evident general clinical improvement. He received a total of 10.5 Gm. of aureomycin over a four-day period and went on to satisfactory convalescence. During convalescence, however, he developed a mild anemia. The admission hemoglobin had been 13.0 Gm. with 4.85 million red cells. Two weeks later, hemoglobin was found to be 10.5 Gm. with 3.55 million red cells. Three weeks from this date the values rose to higher than the admission level.

Cold agglutinins were negative during the acute phase of the disease but rose to 1:1024 during convalescence. Thus, the diagnosis seems established and improvement followed promptly the institution of aureomycin therapy after a penicillin failure. The significance of the anemia is not clear. In this particular patient, there

but believed this was due to the vehicle rather than the drug. It has not been noted in other patients treated orally.

CASE VII. (Patient of Dr. H. Tarnöwer.) A forty year old white male with fever, cough and malaise, and signs of bilateral pneumonitis was treated at home for eleven days. On the seventh day of his illness a white count was 6,400, with 56 per cent polymorphonuclears. During this period his fever ranged from 99° to 103°F., being mainly around 101°F., and he had an interrupted course of intramuscular penicillin, 300,000 units a day for five days, without effect. On October 1st, the eleventh day of the disease, he was admitted to the hospital. At this time his temperature was 101°F., pulse 84, respirations 20. He appeared acutely but not gravely ill and had a paroxysmal cough. Sputum revealed no pathogens. A chest x-ray at this time showed a patchy pneumonitis in both lower lung fields, more marked on the left. Aureomycin treatment was begun immediately with an initial dose of 1.5 Gm. to be followed by 1.0 Gm. every six hours.

The following day he appeared clinically improved and his temperature was a degree lower. It reached normal forty-eight hours after the commencement of therapy and convales-

cence was uneventful. On the third and fourth hospital days the daily dose of aureomycin was reduced to 3 Gm. and then the drug was discontinued. Cold agglutinins on October 2nd were positive in a titer of 1:128. Chest x-ray on October 9th showed complete clearing of the pneumonitis.

complexity and the difficulty of drawing any satisfactory conclusions from it. In brief, a fifty-four year old woman was first seen apparently in extremis after sixteen days of pneumonia which by this time involved both lungs extensively. Cold agglutinins at this time were 1:512 so that the diagnosis seemed established; but

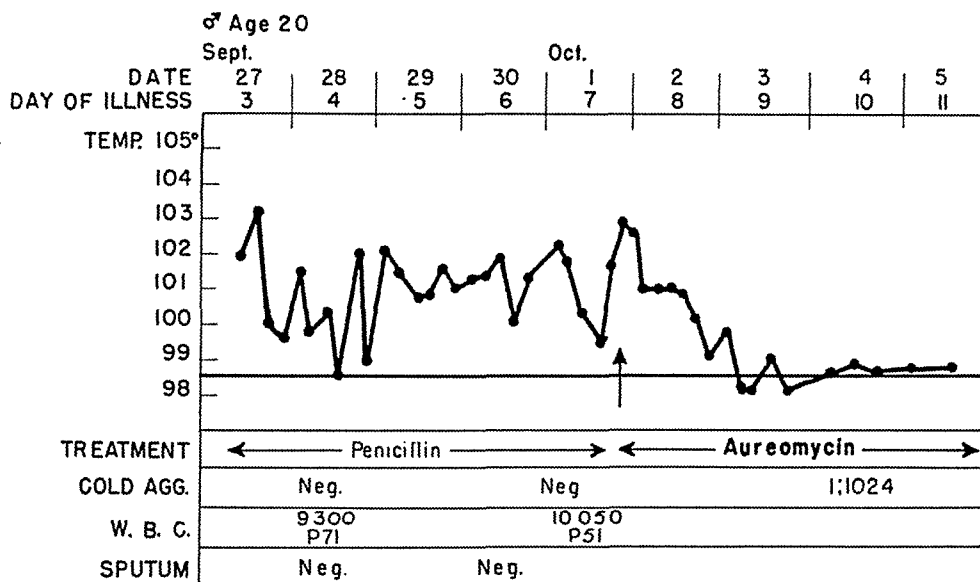


FIG. 5. Chart of Case VI.

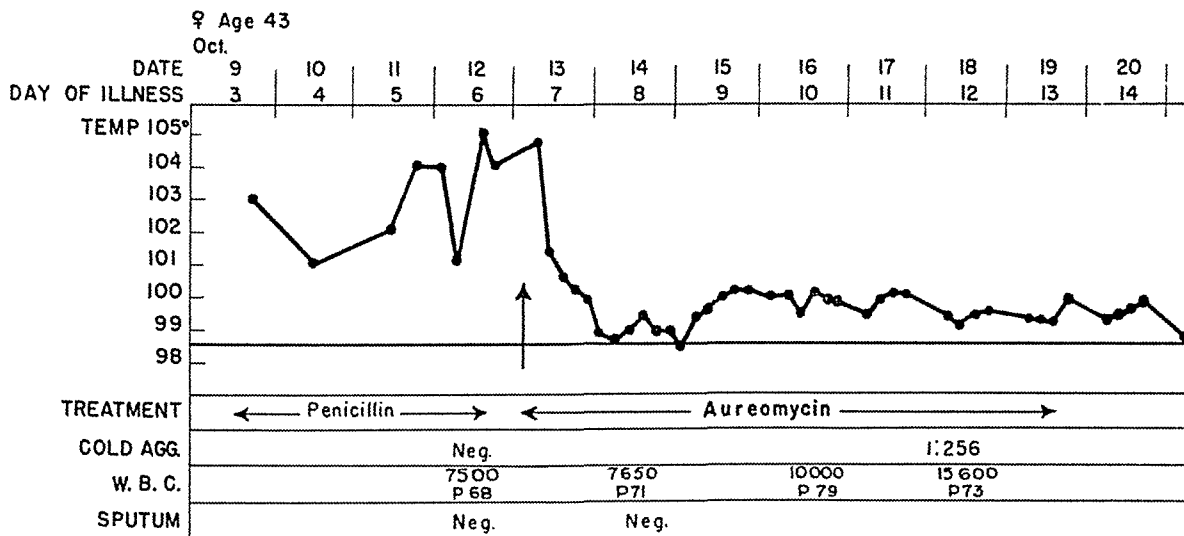


FIG. 6. Chart of Case IX.

This was a rather indolent case of atypical pneumonia, proven by positive cold agglutinins, which seemed to be getting slightly worse at the end of eleven days' treatment with bed rest and penicillin. Following institution of aureomycin therapy rapid clearing of signs and symptoms took place.

CASE VIII. (Patient of Dr. M. Lipkin.) This case will not be presented in detail owing to its

as we had not yet treated anyone who had been ill so long or was in such critical condition, aureomycin was given with no very sanguine hope of success. For the next sixteen hours her condition worsened but then took a turn for the better. Slight but definite improvement seemed to be maintained for the ensuing forty hours at the end of which time her temperature was down to 99.2°F.

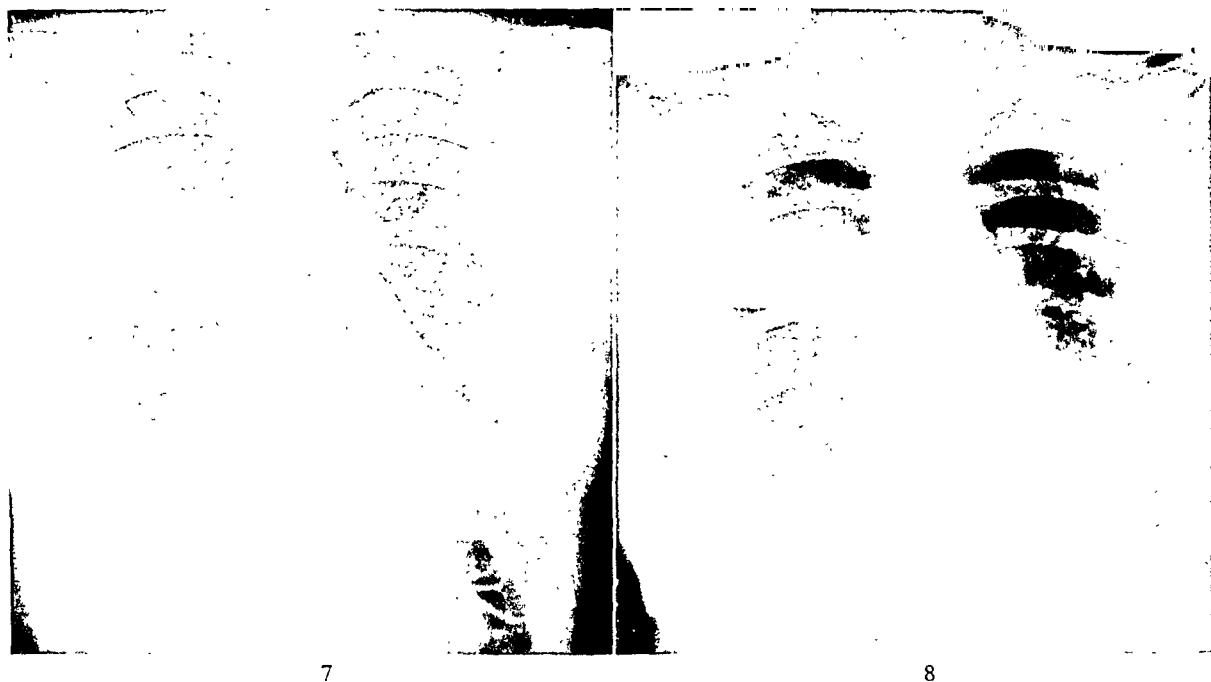


FIG. 7. Case IX, film of the chest taken on October 12th, the day treatment was started, shows a band-like density in the right lung, together with some patchy involvement.

FIG. 8. Case IX, x-ray taken three days later; although temperature was down and clinical improvement had taken place, there is little change to be seen in the appearance of the lesion. Five days after this substantial clearing was noted by x-ray.

Unfortunately, this was one of the two cases in which nausea and vomiting were a most unpleasant concomitant of the drug. At this time while out of the oxygen tent for a fairly brief period, the patient went into anoxic collapse with pulmonary edema and apparently both cardiac and respiratory failure. For some hours the situation was desperate but she gradually rallied. Aureomycin was discontinued so as not to re-induce vomiting. For the next four days the problem was one of treating extreme pulmonary insufficiency. Then, on the fifth day following the collapse although her general condition was improved, her temperature began to rise and there was some clinical evidence of reactivation of the pneumonitis. Aureomycin was then started again; this time she tolerated the drug much better and over the ensuing three days her temperature fell and she improved once more. From this point on, recovery from the pneumonia progressed slowly but steadily although a complicating thrombophlebitis occurred in the right leg. Because of the complicated nature of the illness and the interruption in the course of aureomycin therapy, it is impossible to assess the precise role of the drug in her ultimate recovery.

CASE IX. (Patient of Dr. H. B. Wilcox, Jr.) A forty-three year old white housewife with an

old history of compensated rheumatic heart disease became ill with sore throat and malaise a week before hospital admission. For four days prior to admission she was under her physician's care at home with temperatures ranging from 101° to 105°F. (Fig. 6.) During this period she developed a racking cough and severe headache, and was treated with penicillin in large doses both intramuscularly and by inhalation, as well as with sulfadiazine, without relief.

On admission she appeared acutely ill and prostrated. Her temperature was 104°F., pulse 100, respirations 24. There were signs of mitral stenosis without evidence of failure. There was some percussion dullness noted over the right chest posteriorly, and slight change in breath sounds, without rales. X-ray revealed the dense, band-like shadow shown in Figure 7. The white blood count was 7,500; polymorphonuclears 62 per cent; urine negative. Sputum showed no pathogens on culture, *Streptococcus viridans* predominating. She was started on aureomycin at 6 P.M. October 12th, 1.5 gm., 1.0 Gm. every six hours to follow.

The next morning the 8 A.M. temperature was still elevated but the patient stated she felt considerably improved. Her fever declined to 101.4°F. at noon, and then fell still further, reaching normal at 4 A.M. the third hospital day.

It remained normal for a day and then rose a little, hovering between 99° and 100°F. for the next week. This patient was the second in our series to show nausea and vomiting with the drug. These symptoms were distressing to the patient but in all other respects she did ex-

the whole period, however, he was receiving intramuscular penicillin, 250,000 units twice a day in aqueous solution. This did not appear to influence the progress of the disease and no pneumococci were cultivated from the sputum obtained on hospital admission.

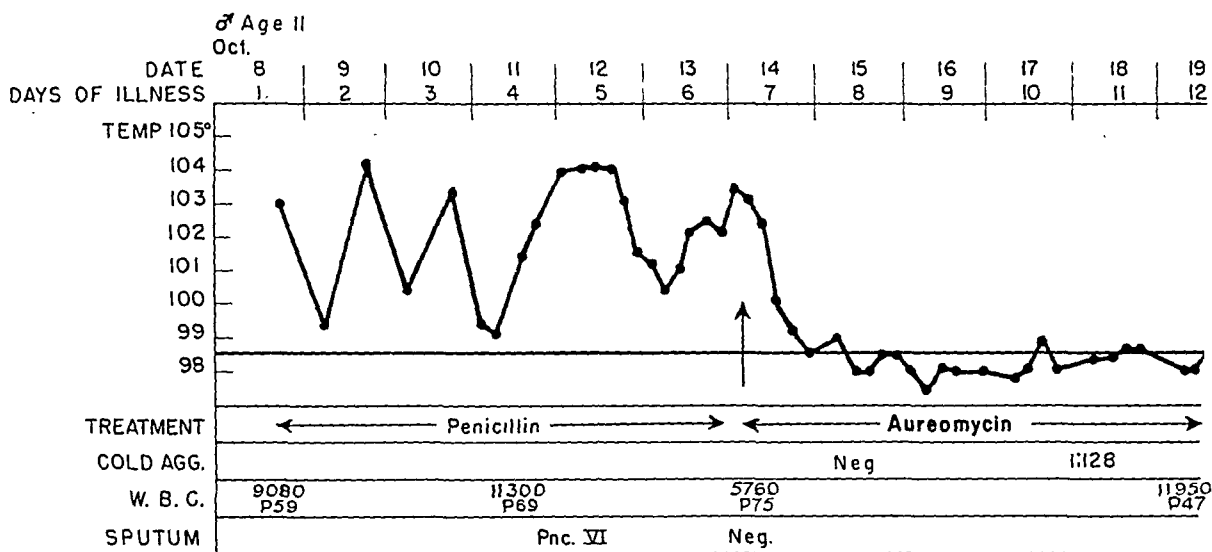


FIG. 9. Chart of Case x.

tremely well. X-ray taken three days after admission showed very little change in the lesion in spite of her marked clinical improvement. (Fig. 8.) On October 19th, however, there was substantial clearing by X-ray. Cold agglutinins which were negative on admission rose to 1:256 six days later. Thus there was no question as to the diagnosis and it was plain that a remarkable improvement took place after the administration of aureomycin. The drug was continued in varying dosage for one week.

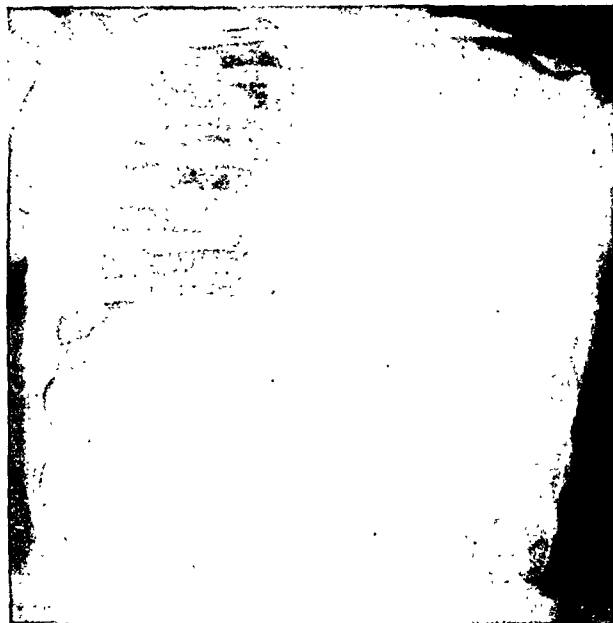
CASE X. (Patient of Dr. Hamilton Southworth.) This patient, the youngest in our series, was an eleven year old white school boy weighing 80 pounds. He became acutely ill on October 8th with malaise, headache and a fever of 103°F. The next day he began to cough and signs of pneumonia appeared at the extreme left base. By October 11th these had progressed to signs of tight consolidation on the left lower lobe. The next day he appeared more toxic and there was evidence of extension of the left upper lobe. The temperature curve during the six days of treatment at home before hospital admission is shown in Figure 9.

On October 9th the white count was 9,080 with 59 per cent polymorphonuclears. On the 12th it was 11,300, with 69 per cent polymorphonuclears, and sputum obtained on this day grew out a type VI pneumococcus. During

He was admitted at noon on October 13th. Examination disclosed an acutely ill boy, coughing and quite cyanotic. There were signs of dense consolidation of the left upper lobe. Over the lower lobe posteriorly the breath sounds were bronchovesicular, with abundant redux crepitus. There was no detectable displacement of the mediastinal structures. His temperature on admission was 102.2°F. After x-ray he was immediately given 0.8 Gm. of aureomycin and placed in oxygen.

His admission white count was 8,760 with 75 per cent polymorphonuclears. X-ray (Fig. 10) showed a complete density occupying the left lung field. From a radiologic point of view there was some indication of atelectasis but the physical findings were those of consolidation.

As indicated in Figure 9, his temperature fell promptly, reaching normal in twelve hours, where it remained thereafter. There was rapid defervescence of the physical signs of pneumonia and a striking relief of all symptoms. He was maintained on aureomycin for five days, dosage being scaled down from 0.6 Gm. every six hours to 0.3 Gm. (his body weight being about 80 pounds). Repeat x-ray, five days after admission, showed complete clearing of the lesion. (Fig. 11.) Cold agglutinins which were negative on October 14th rose to 1:128 four days later, the eleventh day of disease.



10



11

FIG. 10. Case x, x-ray taken on October 14th shows massive involvement of left lung.
FIG. 11. Case x, five days later the lesion has disappeared.

It may be objected that the x-ray and physical signs in this case were most unusual for atypical pneumonia. Moreover, a type vi pneumococcus was isolated from the sputum on one occasion. On the other hand, lobar densities have been described in atypical pneumonia and we believe that the low white count, the failure to respond to penicillin in adequate dosage and the sharp rise in titer of cold agglutinins establish the diagnosis.

SUMMARY AND CONCLUSIONS

1. Ten patients with what we believe to be atypical ("virus") pneumonia have been treated with aureomycin orally. Of these eight showed the development of cold agglutinins at the expected period in the disease.

2. In nine patients the temperature became normal twelve to forty-eight hours after the drug was first administered, with corresponding improvement in their general condition. In two of these treatment was discontinued at this time, and what appeared to be a recrudescence of the disease took place. In the other seven cases treatment was maintained and uneventful recovery ensued.

3. One patient, a fifty-four year old woman who appeared in extremis at the time treatment was initiated, ultimately recovered but we do not feel justified in drawing any conclusions as to the effect of the drug in her case.

4. No important toxic side effects of the aureomycin were noted.

5. The data submitted in this report suggest that aureomycin may have an antiviral effect against the agent which causes atypical pneumonia in man.*

REFERENCES

1. DUGGAR, B. M. *Proc. N. Y. Acad. Sc.*, in press.
2. HARNED, B. K., CUNNINGHAM, R. W., CLARK, M. C., COSGROVE, R., HINE, C. H., MCCAULEY, W. J., STOKEY, E., VESSEY, R. E., YULA, N. N. and SUBBAROW, Y. (In press.)
3. WONG, S. C. and COX, H. (In press.)
4. BRYER, M. S., SCHOENBACH, E. B., CHANDLER, C. A., BLISS, E. A. and LONG, P. H. Aureomycin, experimental and clinical investigations. *J. A. M. A.*, 138: 117, 1948.
5. WRIGHT, L. T., SANDERS, M., LOGAN, M. A., PRIGOT, A. and HILL, L. M. Aureomycin: a new antibiotic with virucidal properties. *J. A. M. A.*, 138: 408, 1948.

* Since this report was submitted, five additional patients with atypical pneumonia have been given aureomycin treatment with very satisfactory results.

Pheochromocytoma with Diabetes and Hypertension*

Report of Two Cases Cured by Operation

A. DE VRIES, M.D., M. RACHMILEWITZ, M.D. and M. SCHUMERT, M.D.

Jerusalem, Palestine

THE characteristic manifestations of pheochromocytoma are paroxysms of hypertension accompanied by headache, palpitation, perspiration, nausea and occasional vomiting. In exceptional cases persistent hypertension has been observed. Occasionally paroxysmal hyperglycemia and glycosuria also have been found. All these signs and symptoms of the disease have disappeared in successfully operated cases, even in those in which the clinical picture resembled that of malignant hypertension. Persistent hyperglycemia and glycosuria associated with pheochromocytoma which disappeared after operation has been described by Duncan et al.¹ and by Green.²

The present report is concerned with two cases of pheochromocytoma, in one of which paroxysmal hypertension and paroxysmal glycosuria were notable features while in the other paroxysmal hypertension and persistent diabetes existed. In both, disappearance of all signs and symptoms followed removal of the tumor.

CASE REPORTS

CASE I. J. J., a forty-one year merchant, was admitted to the Hadassah Hospital on April 4, 1946, complaining of attacks of headache, pain in the precordial region, palpitation, dizziness and profuse perspiration. At the age of twenty-four he contracted syphilis and was treated with salvarsan. Subsequently, repeated blood examinations for lues were negative. In 1941 his blood pressure was found to be 160/90

mm. Hg. In the same year he suffered an attack of anginal pain; the blood pressure at that time was 160/100 mm. Hg. The same blood pressure was noted again in May, 1945. In June, 1945 he had a severe attack of pain in the chest, radiating to the left arm, accompanied by perspiration, dizziness and palpitation. He was admitted to a hospital where the diagnosis of myocardial infarction was made and which was confirmed by electrocardiographic examination. During his three months' stay in that hospital he had repeated attacks of cardiac pain with headache and perspiration during which systolic blood pressure readings of 200 mm. Hg were registered; after the attacks the blood pressure returned to normal. In October, 1945 he was transferred to another hospital where he was confined to bed for about five months with complaints of anginal pain, headache, sleeplessness and constipation. He also had frequent attacks of severe headache with tinnitus, dizziness and profuse perspiration accompanied by waves of heat in the face. The blood pressure fluctuated between normal levels and 200/130 mm. Hg during the attacks. The urine contained a small amount of albumin, sugar up to 5.7 per cent and occasional traces of acetone. The blood sugar was elevated, the highest values being 400 mg. per cent; 40 to 80 units of regular insulin were needed to control the diabetes. On the basis of these findings a tentative diagnosis of tumor of the adrenal medulla was made but kidney x-rays were not confirmatory. After leaving the hospital his condition grew worse and he was admitted to our hospital in April, 1946 because of aggravation of his diabetic condition.

* From The Department of Internal Medicine, Division B. The Hadassah Rothschild University Hospital, Jerusalem, Palestine.

On admission the nutritional state was found to be poor. The patient was restless, perspired profusely and had an acetone breath. The color of his face was strikingly red, there was no peripheral edema and no abnormal pigmentation of the skin. The pulse was 100 and regular. The heart was found slightly enlarged to the left; there were no signs of congestive failure. Examination of the abdomen was negative. The blood pressure was 200/140 mm. Hg. The urine contained a moderate amount of albumin and a large quantity of sugar and acetone. The blood sugar was 400 mg. per cent. The patient was given 100 units of regular insulin during the first twenty-four hours, after which the acetoneuria disappeared and the blood sugar came down to 260 mg. per 100 cc.

During his stay in the hospital the patient complained of weakness, severe headache and dull precordial pain, palpitation, dizziness, bursting headache, tinnitus and severe perspiration. The blood pressure showed marked fluctuations. The slightest excitement, even application of the blood pressure cuff, would provoke a rise in blood pressure up to levels of 200/140 at which it sometimes remained a few minutes only to fall suddenly to very low levels (80/60 mm. Hg). Profuse perspiration appeared constantly whenever the blood pressure fell. The paroxysms appeared quite irregularly. Occasionally they appeared repeatedly during a single day, at other times there were intervals when there were no particular subjective complaints and the blood pressure was constantly normal.

Fasting blood sugar values varied from 120 to 260 mg. per cent. Following admission, on a diet containing 120 Gm. of carbohydrate, 60 to 90 Gm. of sugar were excreted daily. On 80 units of insulin daily, glucose tolerance was improved and the diabetes was controlled; the carbohydrate intake was increased to 200 Gm. a day. Frequent blood sugar determinations during the paroxysms of hypertension revealed values varying from 130 to 230 mg. per cent. In paroxysm-free intervals of several days' duration the severity of the diabetes did not change and the same amount of insulin had to be given.

Other laboratory findings revealed the following: Blood: hemoglobin, 15.5 Gm. per cent; red cells, 5,250,000 to 5,900,000/mm.³; packed red cell volume, 43 to 52 per cent; leukocytes, 12,000 to 15,600/mm.³. Sedimentation rate, 17 hours (Linzenmeier's method). Blood urea,

28 mg. per cent; cholesterol, 450 mg. per cent. Kidney function: urea-clearance, 55 per cent (standard clearance test of van Slyke). Eye fundi: narrowing of the arteries, fluctuations in caliber; increased light reflex, arteriovenous compression, hemorrhages. Electrocardiogram: left axis deviation; T₁ and T₂ isoelectric; T₃ slightly positive, T₄ negative.

The unusual fluctuations of blood pressure, attacks of perspiration, the throbbing headache and palpitation and the disturbance in the carbohydrate metabolism were compatible with the diagnosis of tumor of the suprarenal medulla. The following procedures were undertaken to verify the diagnosis: Pressure on the loins: the effect was not conclusive; there was a rise in blood pressure from 110/80 to 160/115 mm. Hg, but it occurred after pressure on the right as well as on the left side. Cold pressor test: the blood pressure rose from 130/100 to 220/150 mm. Hg.

Histamine test (Roth and Kvale):³ after the intravenous injection of 0.075 mg. of histamine hydrochloride the blood pressure rose from 130/100 to 250/170 mm. Hg, lasted ten minutes and, at the same time, the patient experienced the complaints usually felt during the paroxysms, even to an increased degree.

X-rays of the kidneys: after intravenous pyelography both kidneys appeared normal in position and size. The pelvis and calices were not distorted and no shadows were seen in the suprarenal region. Planigraphy revealed a normal left kidney; the upper border of the right kidney was not sharply visualized in the various sections.

Because of the latter finding and the fact that tumors of the adrenal medulla occur more frequently on the right side than on the left, the right side was explored on May 13, 1946, by Professor F. Mandl. A tumor of tangerine size was found in the region of the right adrenal gland and removed.

The following observations were made during and immediately after the operation: With the institution of ether anesthesia, the blood pressure rose from 130/100 to 200/150 mm. Hg. Manual pressure on the tumor *in situ* raised the blood pressure to 250/160 mm. Hg. Later, at the time of ligation of the blood vessels, it rose to 300/190. Immediately after removal of the tumor the blood pressure fell to 120/90 and then to 95/80. After 0.25 mg. of epinephrine intravenously and two ampules of supracort intramuscularly the blood pressure rose to 170/130 for a

few minutes and then came down to 115/90. Ten minutes after the operation the patient suddenly went into shock and the blood pressure fell to zero; 0.05 Gm. of ephedrine administered intravenously raised the blood pressure to 100/75. During the day of the operation an intravenous infusion of saline and isotonic glucose was instituted with a total amount of 0.6 Gm. ephedrine. In addition four ampules of supracort were given intramuscularly. The blood pressure was stabilized at 110/80.

Together with the glucose, insulin was administered during the day of the operation and the day after in a total amount of 90 units. During this period the blood sugar fluctuated between 150 to 230 mg. per cent and then became normal at which point it remained while the patient was on a normal diet without insulin.

The pathologic report disclosed the following: Macroscopic examination revealed that the specimen consisted of a rounded, slightly elongated body about 3 by 4 by 6 cm. in size and 30 Gm. in weight. In its greater part it was covered by a thin, transparent, fibrous capsule. In one place the capsule was torn and a friable mass of brown-reddish color protruded from underneath. The intact surface of the specimen was studded with nodular elevations of variable size. Cut surface revealed the greatest part of the specimen to be composed of the same friable and disintegrated mass just mentioned which could be removed with ease, thus leaving a large cystic space. The remaining tissue was a uniformly dark reddish-brown color. At one pole of the specimen there was a portion of bright yellow tissue which could be easily separated; it presented the aspect of a round normal adrenal cortex but on cross section no typical medulla could be detected.

Microscopic examination showed that the tissue in the solid portion of the tumor was composed of large epithelium-like cells which lay within a stroma consisting of thin-walled blood vessels and capillaries and only sparse argentophile fibers which extended from the adventitia of some of these vessels. The large cells formed densely packed sheets and adjacent to some blood vessels they were found in palisade arrangement converging toward the vessel. The cells were fairly uniform with a clear eccentric nucleus. The cytoplasm was palely eosinophilic and granular. There were scattered foci of necrosis which contained scattered

nuclear fragments. In the vicinity of the cystic interior of the tumor such necrotic foci were fused together over wide areas. Sections of material after fixation in Mueller's fluid: a diffuse brown stain was prominent in the necrotic areas in the wall of blood vessels and in the cytoplasm of a great number of large vacuolated cells. A section from the adrenal gland adjacent to but separated from the tumor showed the cortex to be regularly built with extensive hemorrhage in the reticulate zone. In place of the medulla chromaffine cells could be distinguished with certainty. There were a number of small round cells with dark nuclei; the central vein was thin-walled in all sections, an isolated bundle of nerve fibers was also seen.

Histological diagnosis: Chromaffine tumor of adrenal medulla.

The adrenalin content of the tumor was determined as follows: A sample of the tumor was extracted with 10 per cent trichloroacetic acid about twenty minutes after extirpation and aliquot portions of the extract were analyzed by the chemical photometric method of Barker et al.⁴ The value obtained, 13 mg. per Gm. tissue, appeared so high that it was decided to repeat the analyses by a biologic method in view of some uncertainty concerning the specificity of the chemical method. In a preliminary experiment the presence of a highly active pressor substance in the extract was confirmed by the rise in blood pressure of a rabbit in urethane narcosis after intravenous injection of an amount of the extract corresponding to about 0.22 mg. adrenalin (calculated from the chemical determination). The quantitative assay was carried out on the isolated intestine⁵ using rat ileum instead of the rabbit ileum of the original method. By comparison with an adrenalin standard the content of the tumor was calculated to be about 7 mg. per Gm., i.e., about one-half that obtained by the chemical method. The total adrenalin content of the tumor weighing 30 Gm. was between 210 to 390 mg. as compared with 3 to 9 mg. of adrenalin in normal human adrenals. The identity of the active substance in the extract was confirmed by the abolition of its action on the intestine by previous addition of ergotoxin. Ergotoxin, 100 γ , abolished the relaxing effect of 1 γ of adrenalin on the isolated rat intestine in a 50 cc. bath. Postoperative complications were pneumothorax on the right side which required removal of air by puncture once, thrombophlebitis of the left leg

and three pulmonary infarctions, twice in the left and once in the right lung. The effects of the operation on the manifestations of the disease are summarized in Table 1.

Comment. This patient was a man of forty-one suffering from attacks of headache,

in addition severe persistent diabetes was present which required 80 units of regular insulin. The diagnosis of tumor of the adrenal medulla was made and confirmed by operation. After removal of the tumor the diabetes and paroxysmal hypertension

TABLE 1

Cas. 1	Before Operation	After Operation
Blood pressure: mm. Hg		
Spontaneous variations.....	80/60-200/140	110/80-135/90
Cold pressor test.....	220/150	170/140
Histamine test (0.075 mg. histamine hydrochloride intravenously).....	250/170	
Ocular fundi.....	Narrow arteries, fluctuations in caliber, increased reflexes arteriovenous compression, hemorrhages; a large hemorrhage near the disc	Slight constriction of arterioles; in some places irregularity of caliber
Kidney:		
Urine: albumin.....	1+	Negative
Function: urea clearance... (standard)	55 per cent	60 per cent
Electrocardiogram.....	T ₁ and T ₂ isoelectric; T ₃ slightly positive; T ₄ negative	1½ months after operation: higher voltage than before; T ₁ isoelectric, T ₂ slightly positive; 2½ months after operation: higher T ₁ slightly positive; T ₂ , T ₃ and T ₄ positive
Blood:		
Hemoglobin.....	15.5 Gm. per cent	13.2 Gm. per cent
Hematocrit.....	43-52 per cent	39 per cent
Red cell count.....	5.25-5.90 millions/mm. ³	4.0 millions/mm. ³
White cell count.....	12,000-15,600/mm. ³	7,000/mm. ³
Sedimentation rate... (Linzenmeier)	17 hr.	3¾ hr.
Blood sugar tolerance curve.....		Fasting: 73 mg. per cent
Ingestion of 60 Gm. glucose.....		½ hr. after ingestion 126 mg. per cent
		1 hr. after ingestion 156 mg. per cent
		1½ hr. after ingestion 129 mg. per cent
		2 hr. after ingestion 92 mg. per cent
		2½ hr. after ingestion 66 mg. per cent
Effect of 0.5 mg. epinephrine subcutaneously on blood pressure.....		initial level 130/90 mm. Hg
		1-2 min. after injection 140/100 mm. Hg
		4 min. after injection 125/90 mm. Hg
Blood sugar.....		initial level 87 mg. per cent
		15 min. after injection 83 mg. per cent
		30 min. after injection 98 mg. per cent
		50 min. after injection 119 mg. per cent
		70 min. after injection 138 mg. per cent
		90 min. after injection 128 mg. per cent

chest pain, palpitation, perspiration, dizziness and tinnitus. There were frequent paroxysms of hypertension, the blood pressure between the attacks being normal. In

addition severe persistent diabetes was present which required 80 units of regular insulin. The diagnosis of tumor of the adrenal medulla was made and confirmed by operation. After removal of the tumor the diabetes and paroxysmal hypertension

CASE II. R. S., a thirty-three year old man whose case was reported in detail elsewhere,⁶ presented the following clinical features: the first symptoms referable to the disease, consisting of attacks of perspiration, started seven years before it was recognized. During the six months prior to the operation attacks of hypertension were observed, the blood pressure rising sometimes to 250/180 mm. Hg. The clinical picture resembled that of malignant hypertension with diffuse, severe vascular changes; the ocular fundi showed the findings typical of hypertensive neuroretinopathy: papilledema, constricted arterioles, with arteriovenous compression, multiple retinal hemorrhages and exudates. The heart was markedly enlarged to the left; the electrocardiogram showed evidence of myocardial damage and coronary artery disease. During the attacks paroxysms of cardiac asthma and pulmonary edema occurred repeatedly. There was also evidence of renal involvement, manifested by albuminuria, reduced concentration capacity and lowered urea clearance test (47 per cent standard clearance). The urine occasionally contained small amounts of sugar. The blood sugar level fluctuated from normal to increased values (300 mg. per cent) obtained during the paroxysms of hypertension. However, once a blood sugar value of 218 mg. per cent was found when the blood pressure was normal. Blood cholesterol was 400 mg. per cent.

A tangerine-sized tumor, removed from the right adrenal region, showed histologically the characteristic features of pheochromocytoma. The adrenalin content of this tumor which weighed 95 Gm. was 2 mg. per Gm. wet tissue.

Following operation, the paroxysms of hypertension disappeared together with the signs of heart failure. The fundal changes regressed rapidly and the papilledema disappeared completely within one month of the operation. At the same time the hemorrhages were resorbed. Narrowing of the retinal arteries has persisted for over one and one-half years. There has been marked improvement in the kidney function. Six months after the operation the concentration capacity was normal and the urea clearance rose from 47 to 72 per cent. The albuminuria disappeared. The glycosuria and hyperglycemia disappeared completely immediately after the operation and the blood sugar tolerance curve showed normal values five weeks after the operation. The blood cholesterol concentration became normal.

Comment. This thirty-three year old male suffered from attacks of perspiration, headache, palpitation, severe dyspnea and paroxysmal hypertension. Severe visual disturbance was present and the ocular fundi showed the findings typical of malignant hypertension. Hyperglycemia and glycosuria occurred, generally coincident with the paroxysms of hypertension. Removal of a tumor of the right adrenal medulla resulted in almost complete restoration to normal.

COMMENTS

In the second case the clinical signs were more characteristic than in the first. Both the hypertension and hyperglycemia were paroxysmal in nature. Although there was no strict relationship between the height of the hypertension and blood sugar level, the highest blood sugar figures were obtained during the paroxysms of hypertension. It is noteworthy that in this case, although normal blood pressure levels were registered during long intervals between the attacks, there were diffuse vascular changes resembling those found in the malignant phase of persistent hypertension. It might be expected that these vascular changes, presumably lasting for many years and also affecting the kidneys, would cause sustained hypertension even after removal of the tumor. This was not the case and except for arteriosclerotic changes in the ocular fundi the evidence of generalized vascular disease disappeared after operation and the blood pressure remained permanently normal.

In Case I the paroxysms of hypertension were usually very short, sometimes lasting for a few minutes only, and there were many days when a rise in blood pressure did not occur at all. At times different blood pressure readings were registered in rapid succession. The increased perspiration was not synchronous with the elevation of the blood pressure but usually appeared when the blood pressure re-attained normal levels. Although the hypertensive seizures were of short duration, there was definite evidence

of widespread vascular sclerosis as manifested by retinal changes and cardiac and renal involvement. In this case operation resulted in marked improvement.

The disturbance of carbohydrate metabolism in this case is of particular interest. Here we are not dealing with paroxysmal hyperglycemia as in Case II but with a type of diabetes indistinguishable from ordinary diabetes. The metabolic disturbance was at times so severe that it constituted the principal clinical feature of the disease. It was then accompanied by severe acidosis, very high blood sugar levels (up to 400 mg. per cent) and glycosuria amounting to 60 to 80 Gm. a day, a condition which required large amounts of insulin. After operation all the signs of diabetes disappeared almost immediately. That excessive amounts of epinephrine were responsible for the diabetes and that no permanent damage was present in the pancreas is well demonstrated by the normal blood sugar tolerance curve obtained two and one-half months after operation.

These observations raise many intriguing questions. Although the action of epinephrine on the circulatory system and on carbohydrate metabolism has been the subject of numerous investigations, the clinical features of pheochromocytoma are still poorly understood. The lack of correlation between hyperglycemia and hypertension in pheochromocytoma is striking. Hypertension, usually paroxysmal and rarely persistent,⁷ is a constant feature in pheochromocytoma. Hyperglycemia, however, is frequently absent. Of fifty reported cases, including our own two cases of pheochromocytoma, in which blood and urinary sugar were studied evidence of transient hyperglycemia and glycosuria was present in twenty-one. In twenty-four cases no disturbance of carbohydrate metabolism was found. In five individuals (including our patient in Case I) permanent diabetes was present; three of these patients (including our Case I) came to operation with resultant complete cure of the diabetes.

A time relationship between hypertension

and hyperglycemia was frequently observed. In some cases, as in our Case II, paroxysms of hypertension coincided with hyperglycemia. Occasionally excessive blood pressure rises were associated only with moderate hyperglycemia or none at all. Perhaps serial blood sugar determinations would have shown a later rise in blood sugar as it is known that after the intravenous injection of epinephrine hyperglycemia appears somewhat later than the rise in blood pressure.¹⁰ It is remarkable that in the case reported by Thorn et al.,⁷ in which persistent hypertension was present for seven years, careful study failed to reveal any diabetic disturbance. On the contrary a flat blood sugar tolerance curve was found.

In cases of pheochromocytoma epinephrine is being produced in excessive amounts. As to its release into the circulation and the factors influencing it no definite facts are available. From the finding of Beer et al.¹¹ and others^{12,13} it follows that the hypertensive paroxysm is associated with hyperadrenalinemia. The degree of hyperadrenalinemia found by various investigators during the hypertensive crises of pheochromocytoma shows considerable variation in the few instances in which it was examined. The lack of unanimity may possibly be explained by differences in the methods used for the estimation of blood epinephrine.¹¹⁻¹³ There are also insufficient data as to the amount of epinephrine circulating in the blood between the attacks. Stroembek and Hedberg¹² in their case found a 1,000-fold increase in blood epinephrine during the paroxysms and a 30-fold increase between the attacks. On the other hand, Espersen and Dahl-Iversen¹³ using a different method found a 4- to 5-fold increase in blood epinephrine during an attack whereas between attacks the epinephrine content was normal or even subnormal. From clinical observations it is known that certain movements and pressure on the kidney region may bring about a hypertensive paroxysm in pheochromocytoma, presumably by producing an increased outpouring of epinephrine. On this basis transient

hypertension and hyperglycemia are easily understood. It is not clear, however, why hyperglycemia is not as constant a feature of pheochromocytoma as the paroxysm of hypertension, especially considering the fact that in animals as well as in man the minimal amount of epinephrine necessary to produce hyperglycemia does not provoke a rise in blood pressure.¹⁴⁻¹⁷

The explanation of persistent diabetes in some cases of pheochromocytoma and of persistent hypertension in others meets with still more difficulties. It has not been possible to produce persistent diabetes or persistent hypertension in animals by continuous administration of epinephrine. Under such conditions the elevated blood sugar and blood pressure begin to decline.¹⁸⁻²⁰ The explanation offered for this is a reflex overproduction of insulin and depression of epinephrine secretion of the suprarenal gland.^{20,21} Another factor may be an increased rate of destruction of the epinephrine injected.²² The theory of suppressed epinephrine secretion is supported by the excessive drop in blood pressure observed in all cases of pheochromocytoma immediately after removal of the tumor and by the subnormal resting values found in Case 1 (80/60 mm. Hg).

In the two cases with persistent diabetes reported by McCullagh et al.⁸ and by Rogers⁹ the resting blood pressure was found to be elevated and to rise to excessively high levels during the paroxysms. It might be assumed that in these cases a continuous excessive secretion of epinephrine took place, producing persistent hyperglycemia and hypertension. The possibility that continuous excessive secretion of epinephrine took place in Case 1 of our series is not warranted by the behavior of the blood pressure. In this patient the hypertension was definitely paroxysmal, the intervening blood pressure even being subnormal while the diabetes was permanently present. This discrepancy cannot be explained by the assumption that disease of the pancreas was responsible since after the operation the signs of diabetes disappeared

completely and a normal blood sugar tolerance curve was obtained. Since the presence of the hypophysis is necessary for the production of hyperglycemia by epinephrine,²³⁻²⁶ one might assume that in this case sustained hyperactivity of the anterior lobe of the hypophysis is induced by the hyperadrenalinemia and that this hyperactivity is abolished when the source of the hyperadrenalinemia is removed. Two additional features observed in Case 1 are of interest: the acidosis and the good response to insulin. This patient was admitted to the hospital in a state of severe acidosis with acetonuria. Acetonuria has also been observed in animals receiving epinephrine.²⁷ In pancreatic diabetes ketosis is explained by an overproduction of ketone bodies in a liver depleted of glycogen, consequent to lack of insulin. In epinephrine diabetes, however, there is no glycogen depletion in the liver. On the contrary, after a short interval following epinephrine injection liver glycogen increases.²⁸⁻³⁰ Epinephrine induces the muscles to produce an increased amount of lactic acid which is transported by the blood stream to the liver where it is converted to glycogen.³¹ This process balances and actually supersedes the glycolytic action of epinephrine on the liver, the net result being hyperglycemia, decrease of muscle glycogen and increase of liver glycogen. Therefore, development of ketosis in pheochromocytoma is difficult to explain except in case of severe depletion of muscle glycogen or if it is assumed that epinephrine accelerates fat catabolism, by direct action in this respect.³²⁻³⁶

The severe diabetes of the first patient before operation was well controlled by insulin. This conforms with the observed antagonism between insulin and epinephrine in animals³⁷⁻³⁹ as well as in perfused organs.⁴⁰⁻⁴¹

SUMMARY

Two cases of pheochromocytoma have been reported. One patient had paroxysmal hypertension and persistent diabetes while in the other patient both hypertension and

diabetes were paroxysmal. In both patients a complete cure was effected by removal of the adrenal medullary tumor. The inconsistency of the symptomatology of pheochromocytoma with the known physiologic and biochemical effects of epinephrine has been pointed out.

REFERENCES

1. DUNCAN, L. E., JR., SEMANS, J. H. and HOWARD, J. E. Adrenal medullary tumor (pheochromocytoma) and diabetes mellitus: disappearance of diabetes after removal of the tumor. *Ann. Int. Med.*, 20: 815, 1944.
2. GREEN, D. M. Pheochromocytoma and chronic hypertension. *J. A. M. A.*, 131: 1260-1264, 1946.
3. ROTH, G. M. and KVALE, W. F. Tentative test for diagnosis of pheochromocytoma. *J. Lab. & Clin. Med.*, 30: 366-368, 1945.
4. BARKER, J. H., EASTLAND, C. J. and EVERS, N. The colorimetric determination of adrenaline in suprarenal gland. *Biochem. J.*, 26: 2129-2143, 1932.
5. BURN, J. H. *Methods of Biological Assay*. London, 1928. Oxford University Press.
6. VRIES, DE A., MANDL, F., RACHMILEWITZ, M. and UNGER, H. Paroxysmal hypertension due to adrenal medullary tumor (pheochromocytoma). Successful operation. *Surgery*, 19: 522-529, 1946.
7. THORN, G. W., HINDLE, J. A. and SANDMEYER, J. A. Pheochromocytoma of adrenal associated with persistent hypertension: case report. *Ann. Int. Med.*, 21: 122-130, 1944.
8. McCULLAGH, E. P. and ENGEL, W. J. Pheochromocytoma and hypermetabolism: report of 2 cases. *Ann. Surg.*, 116: 61-75, 1942.
9. ROGERS, E. Paroxysmal hypertension associated with a ganglioneuroma of the suprarenal medulla. *Am. Heart J.*, 8: 269-274, 1932.
10. CORI, C. F. Mammalian carbohydrate metabolism. *Physiol. Rev.*, 11: 143-276, 1931.
11. BEER, E., KING, F. H. and PRINZMETAL, M. Pheochromocytoma with demonstration of pressor (adrenaline) substance in blood preoperatively during hypertensive crises. *Ann. Surg.*, 106: 85-97, 1937.
12. STROMBECK, J. P. and HEDBERG, T. P. Tumor of suprarenal medulla associated with paroxysmal hypertension. Report of case preoperatively diagnosed and cured by extirpation after capsular incision. *Acta chir. Scandinav.*, 82: 177-189, 1939.
13. ESPERSEN, T. and DAHL-IVERSEN, E. The clinical picture and treatment of pheochromocytoma of the suprarenal. Two own cases with paroxysmal hypertension, improved by treatment with methylthiouracil and cured by surgical intervention. *Acta chir. Scandinav.*, 94: 271-290, 1946.
14. CORI, C. F. and BUCHWALD, K. W. Effect of continuous intravenous injection of epinephrine on the carbohydrate metabolism, basal metabolism and vascular system of normal men. *Am. J. Physiol.*, 95: 71-78, 1930.
15. TRENDLENBURG, P. and FLEISCHAUER, K. Ueber den Einfluss des Zuckerstiches auf die Adrenalin Sekretion der Nebennieren. *Ztschr. f. d. ges. exper. Med.*, 1: 369-396, 1913.
16. CORI, C. F., CORI, G. T. and BUCHWALD, K. W. The mechanism of epinephrine action. Changes in blood sugar, lactic acid and blood pressure during continuous intravenous injection of epinephrine. *Am. J. Physiol.*, 93: 273-283, 1930.
17. CORI, C. F. and CORI, G. T. The influence of constant intravenous injection of epinephrine on blood sugar of rats. *Proc. Soc. Exper. Biol. & Med.*, 27: 560-561, 1930.
18. CORI, C. F., FISHER, R. E. and CORI, G. T. The effect of epinephrine on arterial and venous plasma sugar and bloodflow in dogs and cats. *Am. J. Physiol.*, 114: 53-68, 1935.
19. MYLON, E., CASHMAN, C. W. and WINTERNITZ, M. C. The relation of adrenaline and of the carotid sinus to the hyperglycemia of shock. *Am. J. Physiol.*, 142: 638-647, 1944.
20. MALMEJAC, J. and DONNET, V. Sur les variations de la glycémie au cours d'injections intraveineuses continuées de petites doses d'adrenaline. *Compt. rend. Soc. de Biol.*, 119: 734-736, 1935.
21. MALMEJAC, J., DONNET, V. and DESANTI, E. Injection continuée d'adrenaline et adrenaline-secretion. *Compt. rend. Soc. de Biol.*, 119: 1152-1154, 1935.
22. HERMAN, H., MORIN, G. and VIAL, J. Sur l'action vaso-motrice des doses infimes d'adrenaline. *Compt. rend. Soc. de Biol.*, 122: 1099-1101, 1936.
23. ASCHNER, B. Ueber die Funktion der Hypophyse. *Pflüger's Arch. f. d. ges. Physiol.*, 146: 1-146, 1912.
24. CORKILL, A. B., MARKS, H. P. and WHITE, W. E. Relation of the pituitary gland to the action of insulin and adrenaline. *J. Physiol.*, 80: 193-205, 1933.
25. COPE, O. and MARKS, H. P. Further experiments on the relation of the pituitary gland to the action of insulin and adrenaline. *J. Physiol.*, 83: 157-176, 1934.
26. DEBODT, R. C., BLOCK, H. I. and GROSS, I. H. Role of anterior pituitary in adrenaline hyperglycemia and liver glycogenolysis. *Am. J. Physiol.*, 137: 124-135, 1942.
27. ANDERSON, A. B. and ANDERSON, M. D. The effect of adrenaline on ketosis in phloridzinized and normal rats. *Biochem. J.*, 21: 1398-1403, 1927.
28. SAHYUN, M. and LUCK, J. M. The influence of epinephrine and insulin on the distribution of glycogen in rabbits. *J. Biol. Chem.*, 85: 1-20, 1929.
29. CORI, C. F. and CORI, G. T. Mechanisms of epinephrine action: influence of epinephrine on carbohydrate metabolism of fasting rats, with note on new formation of carbohydrates. *J. Biol. Chem.*, 79: 309-319, 1928.
30. CORI, C. F. and CORI, G. T. Mechanism of epinephrine action: influence of epinephrine on utilization of absorbed glucose. *J. Biol. Chem.*, 79: 343-355, 1928.
31. CORI, C. F. and CORI, G. T. Glycogen formation in the liver from d- and l-lactic acid. *J. Biol. Chem.*, 81: 389-403, 1929.
32. BOOTHBY, W. M. and SANDIFORD, I. The calorogenic action of adrenaline chlorid. *Am. J. Physiol.*, 66: 93-123, 1923.
33. DONTCHEFF, L. and SCHAEFFER, G. Evolution de

- l'extra chaleur de l'action dynamique spécifique des protides chez le lapin a la neutralité thermique et a basse temperature. *Compt. rend. Soc. de Biol.*, 127: 1290-1293, 1938.
34. DONTCHEFF, L. and SCHAEFFER, G., Les protides ne sont pas utilisés dans la thermogenese reflexe de rechauffement. *Compt. rend. Soc. de Biol.*, 127: 1294-1295, 1938.
35. NEUFELD, A. H. and ROSS, W. D. Blood ketone bodies in relation to carbohydrate metabolism in muscular exercise. *Am. J. Physiol.*, 138: 747-752, 1943.
36. BLIXENKRONE-MOLLER, N. Respiratorischer Stoffwechsel und Ketonbildung der Leber. *Ztschr. f. physiol. Chem.*, 252: 117-136, 1938.
37. ISSEKUTZ, B. VON. Beitræge zur Wirkung des Insulins. I. Mitteilung: Zuckerbildung der ueberlebenden Froschleber. *Biochem. Ztschr.* 147: 264-274, 1927.
38. NAYER, P. P. De l'equilibre insuline-adrenaline. *Compt. rend. Soc. de Biol.*, 111: 1049-1051, 1932.
39. BOUCKAERT, J. P. and DE DUVE. The action of insulin. *Physiol. Rev.*, 27: 39-71, 1947.
40. ISSEKUTZ, B. VON. Beitræge zur Wirkung des Insulins. II. Mitteilung: Insulin-Adrenalin Antagonismus. *Biochem. Ztschr.*, 183: 283-297, 1927.
41. BORNSTEIN, A. and GRIESBACH, W. Ueber Zucker-verbrennung der kuenstlich durchbluteten Leber. Wirkung von Adrenalin und Pilocarpin. *Ztschr. f. d. ges. exper. Med.*, 37: 33, 1923.

Arteriosclerosis^{*}

A Statement of the Problem

RICHARD GUBNER, M.D. and HARRY E. UNGERLEIDER, M.D.

New York, New York

"Thus do interpretations throng and clash, and neatly equal the commentators in number. Yet possibly each one of these unriddlings, with no doubt a host of others is conceivable; so that wisdom will dwell upon none of them very seriously."
James Branch Cabell in "Jurgen"

THAT some broad frame of reference is needed in the problem of arteriosclerosis is patent from the widely divergent concepts of its pathogenesis. The many facts which are known about arteriosclerosis have been subject to the most varied interpretations. Thus it is held that arteriosclerosis is a progressive and irreversible affection of the arteries and "one of the indispensable penalties of living,"¹ whereas evidence exists that arteriosclerosis is reversible²⁻⁶ and is not necessarily associated with aging.⁷ The lipid infiltration of the arterial intima and subintima which constitutes the basic pathologic lesion of arteriosclerosis is variously regarded as due to imbibition from the blood stream;⁴ as the result of invasion of the subendothelial layer of the artery from the bloodstream by foam cell lipid-laden macrophages wandering from the liver;⁸ as a consequence of extravasation of serum and of hemorrhage from the arterial vasa vasorum;^{9,10} as a secondary reactive process to injury of the intima which is, according to this view, the primary lesion of arteriosclerosis;⁶ as necrotic debris of degenerated subintimal tissue;¹¹ and as due to local production of lipid consequent to disorganization of the intima resulting from mechanical strain of the arterial wall.¹²

Divergent opinions are held regarding the permeability of the arterial intima. It is considered on the one hand that decreased permeability of the intima due to coating of the endothelium by a lipid film, with impaired nutritional supply to the arterial wall, is of prime importance in the genesis of arteriosclerosis,¹³⁻¹⁴ and on the other hand that increased permeability of the intima favors the penetration of lipid.^{15,16} The latter view considers that a loosening of the connective tissue ground substance of the intima occurs as part of the colloidal aging process or is due to mechanical strain.

The relation of the serum lipids to atherosclerosis is also a subject of contention. Atherosclerosis is regarded by some as due to hypercholesterolemia,^{17,18} whereas it is stated that there is "no valid reason for believing that a disturbance of cholesterol or lipid metabolism plays any part in the etiology of human arteriosclerosis,"⁶ and it is claimed that hypercholesterolemia is a complication rather than an etiologic factor in arteriosclerosis.¹⁹ Elsewhere it is considered that "atheromatosis is not due to hypercholesterolemia but due rather to a disturbance in the stabilization of the colloid state of cholesterol in the blood,"¹³ with factors favoring the precipitation of cholesterol in plasma and tissues. Whereas

* From the Medical Department, Equitable Life Assurance Society of the United States, New York City, and the Department of Medicine, Long Island College of Medicine, Brooklyn, N. Y.

many have considered cholesterol alone as important in the genesis of arteriosclerosis, other serum lipids have been shown to play a significant role as well.²⁰⁻²³ Factors associated with arteriosclerosis, such as diabetes mellitus (with its frequently attendant hyperlipemia) and hypertension, are considered both causes²⁴⁻²⁷ and consequences^{1,19,28-31} of arteriosclerosis. The role of the arterial vasa vasorum which has recently attracted much attention has been interpreted both as a prime factor in the genesis of arteriosclerosis^{9,10,32} and as a secondary reactive phenomenon.^{33,34} Opposite views are held too concerning the primary⁸ versus the secondary⁶ significance of the "foam" cells which are conspicuous in the histology of atherosclerotic lesions. Apart from differences in opinion as to the significance of foam cells there is no unanimity regarding their origin. Whereas they are considered to be of phagocytic nature,^{6,8} it has been suggested that they are endothelial cells which become fat-laden and penetrate into deeper layers of the artery where they disintegrate directly into atheromatous masses.³⁵

In the face of such extremes of opinion it is not possible to define with exactitude the relative importance and mechanisms of operation of the various factors which have been demonstrated to bear a relation to arteriosclerosis. Evident it must be, however, that there is no single cause, *sui generis*, of arteriosclerosis. Rather the evolution of the arteriosclerotic lesion appears to be due to multiple factors mutually interrelated in a dynamic mechanism. Although broad gaps exist, the knowledge at present available permits the tentative formulation of a concept of the genesis of arteriosclerosis integrating the various morphologic, physiologic and biochemical aspects.

The artery, no less than other specialized tissues, is an organ with a metabolically active parenchyma (the muscle cells), supporting tissue (fibroblasts and elastic and collagen fibers) and an intercellular medium through which nutrition is brought and waste products are removed. It is the unique arrangement of the circulation

through the intercellular medium of the artery which appears in large measure to provide the background for arteriosclerosis. The subject of nutrition of the vascular wall has been admirably reviewed by Ramsey.³⁶ There appears to be general agreement that the arterial wall is normally nourished from two sources. The adventitia and outer portion of the muscular media are supplied by vasa vasorum from the outer surface of the vessel. The inner layers of the arterial wall, including most of the media, derive their nourishment from the blood flowing within the lumen of the vessel, for the most part by direct diffusion across the intact intimal endothelial membrane. The studies of Petroff,³⁷ Lange,³⁸ Anitschkow¹⁶ and Iwanov³⁹ indicate that normally a constant stream flows through the walls of the large arteries in the direction from lumen to adventitia. Water, salts, dextrose and other blood constituents enter the subintimal tissue spaces in the course of this nutritive process to the vascular wall. Colored substances such as bile pigments and colloidal dyes, e.g., trypan blue, can readily be observed to enter the arterial wall from the blood stream. Lipoids, too, penetrate the intima and are transported externally through the media to be removed by the lymphatics of the adventitia.⁴⁰ After passing through the endothelial membrane, the blood transudate, i.e., intercellular fluid, penetrates the entire thickness of the arterial wall and is transported off by the lymphatics and veins of the adventitia.

The same factors which determine the composition and circulation of the intercellular fluid in other tissues of the body operate in controlling fluid movement through the artery. These include the vascular filtration pressure (intravascular pressure minus osmotic pressure of blood), composition of the blood, permeability of the endothelial membrane, physical state of the intercellular medium and barriers to fluid flow, venous and lymphatic removal of the intercellular fluid and adjuvant factors aiding movement and removal of components of the intercellular medium, such as gross

movement of the part and phagocytic activity. The quantitative effects of these several factors differ greatly, however, in relation to their action in determining the intercellular composition and circulation elsewhere in the body.

INTRAVASCULAR FILTRATION PRESSURE

Whereas the filtration pressure in all other tissues of the body is the relatively low capillary blood pressure, in the arteries the arterial blood pressure itself, which is many times the magnitude of the capillary pressure, determines in large part the movement of fluid across the endothelial intimal membrane into the subendothelial tissue spaces. Consequently, no such delicate balance between intravascular filtering pressure and the colloid osmotic pressure of the blood obtains as in the capillaries. The arterial pressure is the dominant factor in determining the penetration of the arterial endothelium by blood constituents. The penetration of substances such as cholesterol may be increased by virtue of this high filtering pressure. It is presumably for this reason that colloids such as cholesterol accumulate to a greater extent in the arterial wall than in other tissues and that the arteries are the most vulnerable organ in the body to degenerative changes.

It is evident a priori, on this basis, that a high level of arterial blood pressure will hasten the deposition of cholesterol and presumably the development of arteriosclerosis. In the presence of hypertension the cholesterol content of the aorta is significantly increased although the serum cholesterol concentration is not elevated.^{41,71} The association of atherosclerosis and hypertension is too well known to require comment. Conversely, it is interesting to note that individuals with hypotension are much less apt to develop arteriosclerosis than those with average normal levels of blood pressure. The study of Hunter⁴² showed that with a blood pressure twenty points less than average, the life expectancy is decidedly better than that of the average population, the actual mortality in this

group being only 71 per cent of the expected, with many fewer deaths from cardiovascular disease. Values in excess of the low optimal level of blood pressure impose an increasing strain on the cardiovascular system, even in the range which has always been regarded as "normal" simply because these are the most common levels. The atherosclerotic changes in the large arteries are in no way qualitatively different in hypertension from the atherosclerosis in the coronary arteries and aorta which develop in the absence of hypertension,⁴³ but the elevated blood pressure accentuates the development of these lesions.

Arteriosclerosis is not a uniform process throughout the arteries of the body but exhibits definite zones of predilection. The regions predominantly involved are those subject to greatest intravascular pressure. The susceptibility of the coronary arteries to arteriosclerosis is best comprehended as the result of the unusual pressure relationships in these vessels. Arterial blood pressure has two components, static or lateral pressure head and velocity head. When blood flow is obstructed, the velocity head component is transformed into static pressure augmenting the lateral pressure exerted against the arterial wall. This is what occurs in the coronary arteries supplying the left ventricle during systole for there is considerable retardation of systolic flow^{44,45} due to the high level of intramural systolic pressure in the left ventricle, particularly in the deeper layers.⁴⁶ The resulting high lateral systolic pressure head in the epicardial extramural segments of the coronary arteries may greatly accentuate the development of atherosclerosis, particularly in the vessels supplying the left ventricle. Intramural systolic pressure in the right ventricle and auricles is lower than in the left ventricle and does not cause any considerable retardation of systolic flow.⁴⁷ It is for this reason that atherosclerosis is less marked in the right coronary artery and circumflex branch of the left coronary artery which supply these chambers to a somewhat greater extent than does the left anterior

descending coronary artery. As shown by Ehrlich, de la Chapelle and Cohn,⁴⁸ the left anterior descending coronary artery regularly "ages" much earlier than do the other coronary rami. The vulnerability of the left anterior descending ramus may most reasonably be attributed to the special pressure relationships in this vessel. Particular evidence for this concept is afforded by the data of Horn and Finkelstein³⁴ which show a striking disparity in the frequency of severe sclerotic changes in the branches of the coronary arteries supplying the left ventricle as compared with a much lower incidence of sclerosis in the branches to the right ventricle. In contrast to the predilection to arteriosclerosis of the main coronary arteries is the almost complete immunity to arteriosclerosis of the immediately contiguous intramyocardial segments of the coronary arteries. This may be attributed in large measure to the high external pressure on the intramural coronary vessels during systole so that the net intraluminal pressure exerted against the vessel wall during systole, at least, is negligibly small or even a minus quantity.

Two other regions of the vascular system exhibit a high incidence of arteriosclerosis and in both the intravascular pressure appears to play a significant role in determining localization. Atherosclerosis is very common in the lower extremities where gravity imposes an increased static (lateral) pressure head. The greater incidence of atherosclerosis in the aorta as contrasted with the smaller peripheral muscular arteries likewise may be attributed to the greater lateral pressure head than velocity head in the large elastic arteries. In the smaller arteries the velocity of blood flow is much greater than in the elastic aortic reservoir and the lateral pressure component is lower. One of the most frequent sites of atherosclerosis of the aorta is in the superior portion of the aortic knob at the junction of the transverse and descending segments of the aortic arch. This is the region most subject to the direct impact of the systolic ejection and the area of the aorta against

which greatest intravascular pressure is exerted. The predilection for arteriosclerosis at this site contrasts with the relative freedom from arteriosclerosis in the ascending portion of the aortic arch which is mobile and moves freely with the heart during systolic ejection. Arterial segments which are fixed, as at points of bifurcation and branching in the aorta, or which are immobilized in bony structures and confined tissues, such as the intracranial arteries, are subject to greater pressure impact and are vulnerable to arteriosclerosis. A striking illustration of the importance of restriction of elastic expansion is seen in the greatly increased degree of arteriosclerosis in the posterior wall of the aorta opposite the prominences of the vertebral bodies contrasting with adjacent segments of the aorta which are not fixed and immobile.¹

Further examples may be cited of the role of intravascular pressure in causing atherosclerosis; among them are arteriosclerosis in the aortic arch proximal to coarctation of the aorta, sclerosis of the mitral valve on the ventricular side, sclerosis of the right ventricular endocardium opposite a patent interventricular septum; and of the pulmonary artery opposite patent ductus arteriosus, sclerotic changes in the veins opposite the fistulous opening in arteriovenous fistula, phlebosclerosis wherever veins are subject to prolonged increase in venous pressure, and particularly arteriosclerosis of the pulmonary artery and its branches secondary to pulmonary hypertension caused by such conditions as mitral stenosis and pulmonary diseases leading to cor pulmonale.¹

PERMEABILITY OF THE ARTERIAL INTIMA

While permeability of the endothelial membrane must be of fundamental importance in determining penetration of lipids to form atheromas, knowledge of this aspect of the problem is still fragmentary. Such information as is available derives from the studies of cellular physiologists on membrane permeability. Even here, as stated by Davson and Danielli,⁴⁹ "of the

permeability of natural membranes to fats and proteins very little is known, despite the physiological importance of these compounds." The endothelial membrane consists of the thin endothelial cells and their product, a binding intercellular cement. There is evidence that the membrane is in large measure a thin lipid layer. The chemical stability of the endothelial membrane, particularly the intercellular cement, controls the permeability of the vessel. The permeability is greatly influenced by many factors. It is increased by lack of oxygen, increased acidity and by many noxious substances such as histamine. It is decreased by thyroid hormone, calcium, ascorbic acid, vitamin P, thiocyanates and caproic acid.^{49,50}

So early a student as Virchow believed that heightened permeability is an important determinant in the genesis of arteriosclerosis. His view that a loosening of the connective tissue ground substance of the intima caused by mechanical strain occurred as a preliminary to the imbibition of cholesterol into the subintima is substantially similar to that later expressed by Aschoff¹⁵ who believed that the changes in the intercellular ground substance are to be attributed to colloidal aging. Other investigators, such as Anitschkow,¹⁶ likewise have considered that areas of heightened permeability are important in determining the localization of arteriosclerosis. It was found by Anitschkow that lipid material is deposited in the subintima in the same regions of the aorta which exhibit greatest permeability to colloidal dyes. Somewhat at variance with this point of view is the theory of Hueper^{13,14} that the atheromatous process is initiated by precipitation of a cholesterol film on the intimal surface causing a reduction in permeability of the vessel wall. Hueper believes that the resulting anoxic injury to the endothelial cells secondarily causes increased permeability of the intimal membrane. Increased permeability produced by injury to the intima leads to the formation of subintimal lipid atheromas.^{14,18}

A clinical example of permeability as a factor in arteriosclerosis may exist in the action of the thyroid hormone on vascular permeability. As shown by Lange,⁵¹ deficiency of the thyroid hormone as occurs in hypothyroidism greatly increases capillary permeability and this is reversed by administering thyroid extract. This observation suggests that increased permeability of the intima (in addition to heightened blood cholesterol which is usually present) may be significant in accounting for the well known increased incidence of arteriosclerosis in myxedema. Thyroid deficiency also favors the development of experimental arteriosclerosis.^{52,53} Administration of thyroid on the other hand prevents the development of arteriosclerosis.^{54,55} This beneficial effect may be due in part to the action of thyroid hormone in decreasing the permeability of the endothelial membrane. Thyroid hormone decreases the amount of lipids, such as cholesterol, in the blood; however, there is some evidence that heightened blood cholesterol may play little or no part in explaining the increased occurrence of arteriosclerosis in thyroid-deficient states.^{56,57} However suggestive, the action of thyroid hormone is much too complex to single out its effect on vascular permeability as its sole relation to arteriosclerosis. Iodides and thiocyanates, which also decrease permeability,⁴⁹ likewise inhibit the development of arteriosclerosis in animals fed cholesterol.⁵⁸⁻⁶¹ Since these substances do not affect the content of cholesterol in the blood or cause resolution of lesions produced by prior administration of cholesterol,⁶² their action, like that of thyroid hormone, may be due to their effect on membrane permeability.

BLOOD COMPOSITION: SERUM LIPIDS

The fundamental role of serum lipids in the genesis of arteriosclerosis is emphasized by experimental production of atherosclerosis in the rabbit, guinea pig, chick and dog by sustained dietary elevation of blood-cholesterol. Particularly important, because

of its close resemblance to human atherosclerosis in the distribution and character of the lesions, is the production of atherosclerosis in the dog by the feeding of cholesterol combined with thiouracil administration.⁵³ Clinically it is well known that there is an increased incidence of atherosclerosis in conditions associated with hypercholesterolemia, such as essential xanthomatosis and other lipoidoses, diabetes mellitus, myxedema and nephritis, particularly in the nephrotic stage. It has been reported by some investigators^{63,64} that the level of blood cholesterol is significantly elevated in a large percentage of cases with arteriosclerosis although this is still open to question.⁶⁵ Of interest as a possible indication of a disturbed cholesterol regulation is the observation that not only are the levels of cholesterol elevated in subjects with coronary arteriosclerosis but the serum cholesterol also fluctuates widely, contrasting with a relative constancy of the serum cholesterol in normal individuals.⁶⁴ In a recent study employing the Schoenheimer-Sperry method for blood cholesterol determination, which is more accurate than older methods, it was reported that 68 per cent of seventy-five patients under sixty years of age with coronary occlusion exhibited hypercholesterolemia, with levels of blood cholesterol exceeding 260 mg. per cent.⁶⁶ Particularly significant is the demonstration of hypercholesterolemia in young individuals with coronary artery disease, subjects in whom other factors contributing to the development of arteriosclerosis are lacking.⁶⁷ Hyperlipemia is also very frequent in younger women with coronary artery disease.⁶⁸ The high incidence of arteriosclerosis in groups subsisting on a high fat, high cholesterol diet, as in obese individuals, American soldiers of World War II⁶⁹ and inhabitants of the Kirghiz Steppe (who consume enormous quantities of mare's milk⁷⁰) contrasts eloquently with the rarity of arteriosclerosis in groups on a low fat, low cholesterol diet, e.g., orientals and Europeans during the period of semistarvation following the first World War.^{4,71}

Whereas hypercholesterolemia of considerable degree predisposes to the development of atherosclerosis, low levels of serum cholesterol appear to confer some protection. In a study recently carried out by the authors* it was found that the incidence of arteriosclerosis of the aorta was approximately the same in (1) individuals with slight degrees of hypercholesterolemia (22 per cent of eighty-three cases, average cholesterol 300 mg. per cent) as in (2) those with "normal" cholesterol concentration (20 per cent of eighty-four cases, average cholesterol 211 mg. per cent); whereas among subjects with low cholesterol levels (3) significantly less arteriosclerosis was found (7 per cent of seventy-seven cases, average cholesterol 160 mg. per cent). The average ages and body builds in these groups were similar, (1) forty-eight years, 7.8 per cent overweight, (2) forty-six years, 8.3 per cent overweight, (3) forty-seven years, 6 per cent overweight. No relation could be demonstrated between cholesterol level and age or weight. These observations suggest that the so-called "normal" cholesterol is in reality a high cholesterol, and that the cholesterol level of the average American population is of such an order as to predispose to the development of arteriosclerosis.

Although several hypotheses have been invoked to explain the presence of cholesterol in arterial atheromas, the simplest and most reasonable view is that of direct imbibition of lipids from the plasma together with other plasma constituents through the intimal endothelium under the influence of the high filtering arterial pressure. Chemical analyses indicating that atheromas are not constituted of cholesterol alone but contain the same lipids as are present in plasma²⁰⁻²³ support this concept. Not only lipids but other macromolecular substances in the colloidal state penetrate through the vascular endothelium into the arterial subintima,

*Ungerleider, H. E., Gubner, R. and Rodstein, M. Clinical significance of blood cholesterol. Presented at the Annual Meeting of the American Society for the Study of Arteriosclerosis, Chicago, Oct. 31, 1948.

such as amyloid^{72,73} and hyaline⁷⁴ which derive in part from the serum proteins. Exogenous agents such as the colloidal dyes Evans blue,⁷⁵ fluorescein and naphthol yellow,⁷⁶ trypan blue and lithium carmine^{77,78} similarly penetrate the vascular endothelium to enter the vessel wall. Atheromatous lesions closely resembling experimental cholesterol atheromatosis and human atherosclerosis have been produced by administration of a variety of macromolecular colloidal carbohydrates,¹³ such as polyvinyl alcohol, methyl cellulose, pectin and acacia which enter the arterial subintima by penetration through the endothelium.

Accepting the hypothesis that cholesterol enters the arterial subintima by direct penetration through the endothelium, the mechanism of this transport still remains to be answered. There are at least two ways in which such penetration might occur. Serum cholesterol exists in large molecular colloidal aggregates or micellae^{79,80} in close association with the serum proteins, particularly the globulin fractions.^{81,82} Serum cholesterol may be precipitated with protein, at least with ammonium sulfate fractionation, and passes graded ultrafilters only in association with and in proportion to protein.⁸³ Evidence exists also that cholesterol and protein pass through natural membranes in close association. The concentration of lipids in transudates bears a direct relation to the concentration of lipids in the serum.⁸⁴ The concentration of lipids in the urine parallels the urinary excretion of protein in conditions of increased glomerular permeability producing proteinuria,⁸⁵⁻⁸⁷ and the same relationship occurs in the spinal fluid in disorders associated with increased spinal fluid protein content.⁸⁸ In view of this close association it seems possible that cholesterol, as well as other serum lipids, enters the vessel wall by penetration together with protein under the influence of the arterial filtering pressure. Tissue utilization of hydrophilic colloids such as protein and lecithin, which hold the hydrophobic cholesterol in colloidal dis-

persion,^{21,89} might lead to precipitation of cholesterol in the arterial wall.

An alternative possibility is that cholesterol precipitation occurs first in the bloodstream before penetration into the vessel wall. Although the tissues of most mammals contain approximately the same amount of cholesterol as the corresponding tissues of man, human blood plasma has a higher cholesterol content than any other species⁹⁰ and normally stands at a level not far from the point of saturation.⁹¹ The solubility of cholesterol in the serum, as determined by Loeper's test,⁹² varies greatly, with a striking decrease in older individuals beyond the sixth decade, particularly, it is claimed, in subjects with arteriosclerosis.^{81,93} Eck and Desbordes⁹³ attribute the finding of normal cholesterol levels in the majority of subjects with arteriosclerosis to inability of the serum to dissolve more cholesterol with resulting precipitation in the bloodstream along the vascular channels. These investigators, as well as others such as Alvarez and Neuschlosz⁹⁴ and more recently Hueper,^{13,14} hold the view that the colloidal stability of cholesterol in blood plasma rather than its concentration is the significant factor in the genesis of arteriosclerosis. Hueper believes that the atheromatous process is initiated by an imbalance of the plasma colloidal equilibrium which he attributes to vibration of the blood column, causing the precipitation on the intima of a cholesterol film which penetrates the endothelium. It is difficult to reconcile this concept with the clinical observation that arteriosclerosis is increased in the nephrotic state, in which condition a greatly increased amount of cholesterol is "dissolved" in the serum as a cholesterol globulin colloid complex.⁹⁵

In the light of present knowledge, regulation of the blood cholesterol appears to offer the most promising approach to the prevention of arteriosclerosis. Analysis of the mechanisms whereby blood cholesterol may be lowered requires a brief resumé of the factors controlling cholesterol metabolism. Although cholesterol plays a determin-

ing role in the genesis of arteriosclerosis it cannot be regarded entirely as a noxious agent. Cholesterol serves important physiologic functions as a constituent of all body tissues, as a precursor of cholic acid and steroid hormones and as a vehicle for fatty acid transfer. Cholesterol metabolism, particularly in relation to its concentration in the serum, is best viewed as an adjunct to fat transport.

Cholesterol in the body derives from two sources, synthesis in the liver and ingested cholesterol in the diet. Synthesis of cholesterol in the body is restricted to the liver, the precursors being simple chemical units such as acetic acid as shown by deuterium tag studies.⁹⁶ Acetic acid derives from fatty acids by the mechanism of β -oxidation with removal of acetyl groups from the β -keto acids. Acetic acid contributes to the formation of the entire steroid molecule, with fully half of the hydrogen atoms and probably half of the carbon atoms furnished by acetate.⁹⁷ Apart from synthesis of cholesterol, the liver regulates steroid metabolism in many ways including the formation of cholic acid from cholesterol,⁹⁸ degradation of steroid hormones and the transfer of fatty acids esterified with cholesterol to phosphatides, with excretion of free cholesterol as well as of bile acids in the intestines via the biliary tract. The daily biliary excretion of cholesterol is at least 0.5 Gm. and of bile acids 2 Gm. The cholesterol in the bile as well as that in the diet is in the free (non-esterified) form.¹⁰⁰ The daily cholesterol intake in the mixed diet of the adult varies from 200 to 360 mg.; on a low-fat diet it ranges from 39 to 109 mg.; whereas fat-rich diets may contain up to 1,400 mg. of cholesterol.⁹⁰

In the intestines cholesterol serves as a major vehicle for the absorption of fatty acids, particularly the highly important unsaturated fatty acids. The mechanism whereby this occurs may be briefly described as follows: fatty acids which are liberated by the action of pancreatic lipase on neutral fat are then esterified with cholesterol by pancreatic cholesterol esterase, which is

activated markedly by bile acids^{101,102} in particular by cholic acid and glycocholic acid.¹⁰³ The esterified cholesterol is transported into the epithelial cells of the intestine, unesterified cholesterol itself being absorbed poorly if at all. To be absorbed, therefore, cholesterol requires the presence of fat, pancreatic enzymes and bile salts. If any of these be lacking, cholesterol absorption is greatly impaired. Thus, in animals on a fat-free diet cholesterol which is administered can be recovered quantitatively in the feces.¹⁰⁴

Fatty acids are absorbed not only as cholesterol esters but by other mechanisms as well. Some neutral fat emulsified by bile is absorbed directly, passing into the lymphatics, but the major portion of fat is hydrolyzed by lipases into glycerol and fatty acids. The shorter chain, water-soluble fatty acids as well as glycerol pass directly into the blood stream. The remaining fatty acids, particularly the unsaturated fatty acids, are assimilated both as cholesterol esters in the manner already indicated and by phosphorylation in the intestinal mucosa to form phosphatides, lecithin being the principal vehicle for fatty acid absorption. Phosphorylation by the intestinal mucosa is an important mechanism for the absorption of fatty acids, as indicated by the finding of radioactive phosphate given orally with fats¹⁰⁵ or intravenously¹⁰⁶ in the phosphatides of the intestinal mucosa. Further indication of the importance of phosphorylation in fatty acid absorption may be afforded by the observation that fat absorption is markedly impaired by iodoacetate and phlorizin which inhibit phosphorylation¹⁰⁷ although this has been denied. The fatty acids of the blood phospholipids represent in large part the fatty acids of newly absorbed fat, i.e., fatty acids in transport.¹⁰⁸

These various mechanisms of fat absorption are mentioned because both in absorption and in transport in the blood stream (as indicated by blood concentration) there appears to be a remarkably constant concentration and division of the various lipid

fractions in any individual, suggesting a dynamic interdependence and relationship. Particularly is this true for the ratios cholesterol/cholesterol esters and cholesterol/phospholipids. Neutral fat which usually comprises the smallest fraction of the fatty acids of the plasma is somewhat more independent and variable.¹⁰⁹ The clinical significance of the close interrelation between the various lipid fractions of plasma lies in the realization that blood cholesterol concentrations must not be considered alone but in terms of lipid metabolism as a whole. The reason for the constancy of the partition of fatty acids between cholesterol esters and phospholipids lies in the regulatory activity of the liver in transferring fatty acids from cholesterol to phosphatides, as will presently be mentioned. Bloor¹⁰² has suggested that the constant relationship between cholesterol and phospholipid is useful to the organism in preserving colloidal equilibrium since phospholipid is hydrophilic and cholesterol is hydrophobic.

The hydrophobic, insoluble cholesterol owes its high concentration in the serum of man to agents which allow it to be carried in colloidal dispersion. Phospholipids, as Bloor has suggested, may be significant in this regard. Even more important is the vehicular role of the blood proteins which combine with the blood lipids to form lipoprotein complexes. Electrophoretic studies have indicated that serum lipids are in large part bound to serum proteins, chiefly in a relatively weak bond. Both cholesterol and phospholipids are present in highest concentration in the α_2 and β globulin fraction.^{81,82} Appreciable quantities are also attached to serum albumin and gamma globulin. Lower fatty acids on the other hand exhibit a high electrostatic affinity for serum albumin as shown by electrophoretic studies.¹¹⁰ The marked increase in serum cholesterol which occurs in the nephrotic state^{95,111} may in part be due to the large increase in α_2 and β globulin in this condition, the increased globulin holding more cholesterol and phospholipid. To some extent the unusually

high α and β globulin peaks in the electrophoretic spectrum in nephrosis, seen also to a lesser degree in hypothyroidism,¹¹² must be attributed to elevated cholesterol itself for on extraction of the plasma with ether, removing lipids thereby from their protein complexes, these large peaks become considerably reduced. The globulin-lipid bond is ruptured by heparin with liberation of the combined lipids and the simultaneous formation of a protein-heparin compound.¹¹³ Since heparin has been reported to cause rapid disappearance of alimentary lipemia in dogs,¹¹⁴ it would be of great interest to determine the effect of heparin on blood cholesterol and phospholipids in clinical hyperlipemia states as a possible means of lowering elevated blood cholesterol.

While the serum proteins by virtue of their binding capacity appear to exercise some influence on the level of the serum lipids, a more dynamic role is played by the liver. In the liver, cholesterol esters, which are formed in the intestine as a vehicle for fatty acid absorption and transport, are transferred to choline phosphatides, i.e., lecithin, in preparation for further stages of fat metabolism. The turnover rate of liver phospholipids is accelerated by choline and its precursors¹¹⁵ whereas the transfer of fatty acids from cholesterol esters is impaired in choline deficiency and in hypothyroidism.¹⁰² The mechanism of action of choline and thyroid hormone are interrelated for choline must be present for thyroxine to exert lipotropic action.¹¹⁶ In fatty livers produced by choline deficiency a great accumulation of cholesterol esters occurs in the liver. Conversely, lipotropic agents such as lecithin, choline, methionine, inositol, betaine and thyroid hormone speed up the removal of fatty acids from cholesterol, allowing the liver to pass free cholesterol into the bile.

It is evident from these remarks that serum cholesterol, functioning as a vehicle for fatty acids, can be elevated by any mechanism which elevates the blood fat. Known mechanisms include: (1) impaired

removal of fatty acids by the liver, e.g., in myxedema and in choline deficiency; (2) increased fat in the diet which causes increased reabsorption of cholesterol spilled into the intestine in the bile; (3) mobilization of fat from fat stores as occurs in starvation¹¹⁷ and when utilization of carbohydrate is impaired, as in severe diabetes and during phlorizin administration.¹⁰⁹ (4) An increased capacity of blood to bind lipids associated with elevated globulin concentration may be partially responsible for hypercholesterolemia such as occurs in the nephrotic state, although other factors doubtless play a part. (5) Increased synthesis of cholesterol by the liver is another mechanism which probably is important in the production of hypercholesterolemia, e.g., in diabetes mellitus in which increased fat utilization may provide a greater acetate pool for synthesis into cholesterol.

Attempts to lower blood cholesterol have been directed principally toward the speeding up of hepatic removal of lipids with lipotropic agents, i.e., augmented transfer of fatty acids from cholesterol esters to phosphatides. Experimentally, lecithin and choline fed to rabbits receiving cholesterol restrict hypercholesterolemia and diminish the incidence of arteriosclerosis in these animals.¹¹⁸ While some success has been claimed with the use of these and other lipotropic agents in lowering elevated blood cholesterol in man,^{119,120} their clinical value is at best limited; for such decreases in serum cholesterol as are accomplished are transitory and are not maintained beyond five weeks despite continued administration of lecithin.¹²¹ It is understandable why lipotropic agents in themselves are relatively ineffective in lowering blood cholesterol. These agents accomplish the removal of fatty acid esters from cholesterol in the liver, allowing free cholesterol to be excreted in the bile. However, the biliary cholesterol is promptly reabsorbed in the intestines, back into the circulation, unless cholesterol absorption is prevented by extreme fat restriction or other measures to be considered.

Actually the bile is not an important medium for excretion of cholesterol.¹⁰² Biliary cholesterol is one phase in the physiologic circulation of cholesterol (intestine → blood → liver → bile → intestines) in its role as an adjunct in fat transport rather than a major excretory pathway of cholesterol. If bile is excluded from the intestines by a biliary fistula or by closure of the bile duct,¹²² large amounts of sterols are still found in the feces, unaccounted for by the dietary intake. The major part of sterol excretion takes place directly into the intestine, particularly the large bowel.¹⁰² Just how this occurs has not been explained but the following mechanism may be advanced as plausible. Cholesterol is not stored in the body as is fat, fatty tissues containing no cholesterol or only minimal amounts.¹²³ However, a considerable repository of cholesterol is present in the leukocytes.^{124,125} With the development of infection, both in animals¹²⁶ and in man,¹²⁷ blood cholesterol falls, the serum cholesterol and lipid content tending to vary inversely with the total leukocyte count in infection.¹⁰² Lymphocytes pass into the intestine in enormous quantities, this being their main pathway of disposal by the body.¹²⁸ Generated (as the greater number of lymphocytes are) in the lipid-rich environment of the mesenteric lymphatics and excreted after circulation in the blood into the intestines, lymphocytes may well provide an important mechanism for excretion of sterols. A considerable amount of cholesterol excreted in such manner may be reabsorbed just as biliary cholesterol. It is apparent that an important phase of cholesterol metabolism is exogenous in the intestinal tract. Attempts to deplete the body of cholesterol by an attack on this exogenous phase of cholesterol metabolism appear, as will be outlined, to offer perhaps greater promise than endogenous methods operating within the body tissues.

Destruction of cholesterol in the body has not yet been shown to occur in any appreciable degree and may be of little physiologic consequence in regulating blood

cholesterol. Cholestanol, the hydrogenation product of cholesterol, is found in small concentration in the blood serum,¹²⁹ and cholestenone, the unsaturated ketone which is the initial stage in degradation to coprosterol, has been isolated in body tissues.¹³⁰ One further endogenous aspect of cholesterol metabolism is of some consequence, however, in determining the level of serum cholesterol. Cholesterol is synthesized in the liver. In view of the constant level of serum cholesterol it is probable that a daily synthesis of approximately 0.3 Gm. occurs in man to offset the average negative balance of this amount.¹⁰² It is quite possible that increased hepatic synthesis of cholesterol may be responsible for hypercholesterolemia in cases in which other factors which are known to elevate blood cholesterol do not appear to play a part, i.e., essential familial hypercholesterolemia. The effect of fat in elevating blood cholesterol may be due not only to promotion of intestinal absorption of cholesterol, but perhaps in even more important measure to supplying large quantities of acetate, a building block of cholesterol. The relative significance of exogenous and endogenous cholesterol in contributing to hypercholesterolemia and atherosclerosis awaits clarification by studies with the isotope technic. Clinical evidence that hepatic synthesis of cholesterol and cholesterol esters has an important bearing on the level of blood cholesterol is afforded by the fact that severe liver disease leads to a decided fall in blood cholesterol, particularly of the esters. It remains to be determined whether hepatic synthesis of cholesterol can be decreased, however, without seriously disturbing other important hepatic physiologic functions. Acetic acid metabolism, which is of fundamental importance in cholesterol synthesis, is profoundly affected by sodium fluoroacetate which, because of its close similarity to acetate, blocks enzyme systems concerned with the utilization of acetate by competitive inhibition.¹³¹ The toxicity of this compound may preclude clinical application for such purposes as decreasing cholesterol

synthesis. Other substances less disturbing to the body economy interfere with cholesterol metabolism, and it may be that an effective agent of sufficiently low toxicity can be employed to decrease cholesterol synthesis. Sulfite, a reagent which blocks aldehyde groups, inhibits sterol synthesis from acetate in yeast but does not impair fat synthesis. Cinchophen in doses which do not ordinarily seriously impair hepatic function causes marked suppression of cholic acid synthesis and excretion;¹³² and cholic acid, it is recalled, derives from cholesterol. Thiocyanate is stated to decrease blood cholesterol, presumably due to its effect on the liver,^{133,134} although elsewhere this action is questioned.^{135,136} Sympathomimetic drugs and calcium salts cause hypocholesterolemia,¹³⁷ and in this connection it is of interest that epinephrine increases fecal lipid excretion.¹³⁸ An interesting reciprocal relation exists between the level of blood cholesterol and urea. Blood cholesterol is decreased in uremia,¹³⁹ and elevation in the blood urea following the ingestion of urea by human subjects is often accompanied by a striking fall in the plasma cholesterol.¹⁴⁰ A direct relationship is stated to exist between the cholesterol content of the tissues and blood and the degree of hydration, i.e., salt content of the body.^{141,142}

Such observations leave no doubt that endogenous mechanisms may influence the level of serum cholesterol but no effective means has yet been found to lower serum cholesterol for sustained periods based on mechanisms operating in the body tissues proper. However, the lowering of blood cholesterol by dietary restriction of fat may, as has already been suggested, be due in large measure to decreased hepatic synthesis of cholesterol consequent to a restriction of the acetate precursor of cholesterol. As has been indicated, cholesterol in its metabolic cycle passes through an external phase in the intestines. This appears to be the most vulnerable site for depleting the body of cholesterol. The mechanisms of attack on the exogenous phase of cholesterol metabolism may be outlined as follows:

A. Decrease Ingested Cholesterol. Dietary restriction of cholesterol, although undoubtedly an adjuvant of some utility in any regimen attempting to lower blood cholesterol, has not been found effective of itself. Little or no effect on the blood cholesterol has been observed in prolonged dietary studies employing very low or very high cholesterol diets.^{143,144}

B. Decrease Absorption of Cholesterol. 1. *By reducing the fat content of the diet:* Fat is important not only in cholesterol synthesis but in cholesterol absorption as well. Hypercholesterolemia occurs after administering fat alone,⁹⁰ the blood cholesterol rising during absorption of fat parallel to the increase in blood fatty acids.¹⁰² As Bloor¹⁰² has pointed out, the part played by the bile in supplying cholesterol to the blood has generally been overlooked, and the cholesterol of the bile, reabsorbed during fat absorption, may be sufficient to explain the increase in blood cholesterol after feeding of fat. Absorption of cholesterol occurs only in the presence of fatty acids. On a fat-free diet the cholesterol given can be recovered quantitatively in the feces.¹⁴⁵ A quantitative relationship has been found between the cholesterol content of the bodies of rats and the amount of fat fed on a constant sterol-poor diet.¹⁴⁶ Likewise the absorption of bile acids is decreased on a low-fat diet.¹⁴⁷ Clinically it has been shown that high-fat diets in diabetics favor and low-fat diets retard the appearance of hypercholesterolemia and arteriosclerosis.²⁶ Significant decreases in blood cholesterol have been observed with the Kempner rice diet which has a very low fat content of approximately 5 Gm.¹⁴⁸ Unless dietary restriction of fat is extreme little or no effect on blood cholesterol can be anticipated.

2. *By exclusion of bile from the intestines:* In view of the fact that considerable cholesterol depletion is effected by a biliary fistula,¹⁴⁹⁻¹⁵² protracted non-surgical biliary drainage might accomplish considerable loss of cholesterol and bile acids. As already observed, the daily biliary excretion of cholesterol is at least 0.5 Gm. and of bile acids 2 Gm.

Increased biliary excretion of cholesterol and temporary lowering of blood cholesterol result from administration of lipotropic agents,¹¹⁹⁻¹²¹ and (it is said) the feeding of powdered leaves of artichokes¹⁵³ and eggplant¹⁵⁴ or injection of their aqueous extracts. Such agents would undoubtedly be more effective in decholesterinization if intestinal reabsorption of the cholesterol excreted via the bile could be prevented.

3. *By interfering with pancreatic enzymes which are necessary for the esterification of cholesterol with fatty acids:* It is of interest to note that in steatorrhea due to pancreatic insufficiency the blood cholesterol is unusually low.¹⁵⁵ Absorption of fat is impaired by quinine¹⁵⁶ and by sodium cetyl sulfate¹⁵⁷ which inhibit lipases, thereby preventing lipolysis of neutral fat into fatty acids. Phosphorylation of fatty acids is an important mechanism for their absorption. As already indicated fat absorption may be markedly impaired by iodoacetate and phlorizin which inhibit phosphorylation.¹⁰⁷ Intestinal phosphate can be tied up and made unavailable for phosphorylation by administering aluminum hydroxide gels, which, in daily dosage of 120 to 160 cc., reduce urinary phosphate excretion by 90 per cent.

4. *By esterifying cholesterol with non-absorbable fatty acids:* Long chain fatty acids are poorly absorbed; arachidic acid of peanut oil, for example, is almost wholly excreted in the feces.¹⁵⁸

5. *By physical means which prevent cholesterol absorption:* It has been shown that 20 cc. of liquid petrolatum taken two or three times daily before meals interferes with the absorption of carotene.¹⁵⁹ It appears possible that the absorption of cholesterol might similarly be decreased and fecal excretion augmented by non-absorbable fat solvents such as mineral oil, or by steroid adsorbing agents such as silica gel.

C. Increase Degradation of Cholesterol in the Intestines. 1. *Bacterial destruction of sterols in the intestine.* This is an important physiologic mechanism for the excretion of cholesterol. Cholesterol which is not esteri-

fied with fatty acids in the intestine to be absorbed is in part excreted unchanged in the feces, the greater amount, however, first being degraded in the colon before excretion. Degradation of cholesterol, which occurs in the body tissues to a negligible degree if at all, is accomplished by putrefactive bacteria in the colon.¹⁶⁰ One must conclude that these bacteria exercise an important physiologic function in augmenting the excretion of cholesterol by degrading it into non-absorbable steroids, principally coprosterol. Different strains of coliform organisms vary greatly in their ability to destroy steroids.¹⁶¹ When the bacterial flora of the colon is decreased by administering succinyl-sulfathiazole, the formation of coprosterol is abruptly halted.¹⁶²

The degradation of cholesterol proceeds by oxidation to the ketone cholestenone followed by reduction to coprostanone and further reduction to coprosterol.¹⁶³ The primary oxidation of steroids to the keto form appears to occur in the cecum through the action of the micro-organisms *Alkaligenes faecalis* and *Escherichia coli*, as shown by studies of cholic acid catabolism.¹⁶⁴⁻¹⁶⁸ The sequence of chemical changes in cholesterol degradation may be represented in the following manner: cholesterol \rightleftharpoons cholestenone \rightarrow coprostanone \rightarrow coprosterol. Coprostanone and coprosterol cannot be absorbed from the intestine and once formed are excreted. Cholestenone, however, can be reconverted to cholesterol. The pathway taken by cholestenone depends on factors in the gastrointestinal tract and on the diet. In dogs fed cholestenone with a biscuit diet most is converted to cholesterol, whereas on a meat diet most of the cholestenone administered is excreted as coprosterol.¹⁶⁹ It is probable that the effect of diet on coprosterol formation is due to the determining influence of diet on the intestinal flora, a high-protein meat diet greatly favoring the predominance of coliform organisms¹⁷⁰⁻¹⁷² which possess the ability to degrade cholesterol. A certain portion of cholesterol is degraded by reduction to dihydrocholesterol which, like coprosterol, is not absorbed and is excreted in the feces.

It appears, therefore, that a high protein diet may afford a means of augmenting the conversion of cholestenone to coprosterol, decreasing the amount of cholestenone available for reconversion to cholesterol. It would appear worth while to explore the possibility of implanting strains of coliform organisms which possess a high capacity to accomplish degradation of cholesterol, since, as already mentioned, there is a marked difference in the ability of various strains of coliform organisms to alter steroids.

2. *Chemical destruction of steroids in the intestine:* The observation that cooked brain administered in the diet, both to rats¹⁷³ and dogs,¹⁷⁴ augments the formation of cholestenone from dietary cholesterol and causes a striking increase in the fecal excretion of coprosterol to fully 80 per cent of the fecal sterols is of great interest. It is believed that the substance which enables the organism to convert such large amounts of cholesterol added to the diet into coprosterol via cholestenone is identical with or allied to the cerebroside phrenosin.¹⁷³ The possibility of augmenting cholesterol depletion in man by this means certainly merits investigation.

Numerous other chemical methods are known which, *in vitro* at least, degrade cholesterol and cholestenone. Thus cholestenone may be formed from cholesterol by the action of selenium dioxide¹⁷⁵ and other oxidizing agents,¹⁷⁶ e.g., cupric oxide.¹⁷⁷ Cholestenone may be fixed by ketone reagents as described by Girard,¹⁷⁶ in particular by the hydrochloride of the hydrazide of betaine. Dinitrophenylhydrazine likewise combines with the unsaturated ketone cholestenone.¹⁷⁵ The aldehyde blocking reagent sulfite has been shown to inhibit sterol synthesis from acetate in yeast.⁹⁷ Cholestenone is reduced chemically by many agents such as aluminum isopropylate.¹⁷⁸ To what degree such chemical agents can be employed *in vivo* remains to be determined.

The reduction of cholesterol, to form dihydrocholesterol which, like coprosterol, cannot be absorbed from the intestines, is

slow and appears to offer less promise than the other methods considered.

It is not possible to predict, *a priori*, which of the several agents considered will be found most feasible or effective in reducing blood cholesterol. It is apparent, however, from the above considerations of cholesterol metabolism that both in endogenous and exogenous phases cholesterol and fat are linked intimately. If cholesterol is the actual culprit in arteriosclerosis, fat is an active accomplice. Not only are cholesterol and fat found together in food sources, but they are integrally associated in intestinal absorption, in transport in the blood stream and in early atheromatous deposits. Perhaps the most important connection is the supplying of acetate by fatty acid breakdown as the major precursor in cholesterol synthesis. Stringent restriction of dietary fat, therefore, appears implicitly indicated in any regimen for lowering blood cholesterol. Experience indicates that slight to moderate dietary restriction of fat is of little value in this regard. If, as appears probable, the cholesterol level of the average American population is at such a high level as to predispose to arteriosclerosis, such a regimen of marked fat restriction should apply not only to individuals with hypercholesterolemia but to the general population as well. This would imply a drastic change in the American diet with far reaching effects on the nation's economy. Before any such program can be urged as a public health measure alternative methods for lowering blood cholesterol should be sought; and it must be more firmly established (1) that low levels of cholesterol indeed protect against arteriosclerosis and (2) whether it is practicable to lower and maintain a low cholesterol level through diet alone.

REMOVAL OF LIPOIDS FROM THE ARTERIAL WALL

The intercellular fluid circulation, which brings nutrients and other constituents of the blood plasma into the vessel wall, is also responsible for their removal. The circulation through the vessel wall can be

observed by following the flow of India ink from the bloodstream across the intact endothelial membrane, through the intercellular spaces of the subintima and media to enter the lymphatics of the adventitia and ultimately the regional lymph nodes.³⁹ Lipoid substances, too, follow this path of circulation and are transported through the arterial wall to be absorbed by the lymphatics.¹⁷⁹ Interference with lymphatic and vasa vasorum drainage of the intercellular fluid causes an accumulation of colloids, such as lipoids, in the arterial wall and impaired nutrition to the cellular elements of the artery, favoring the development of atherosclerotic and degenerative changes. This has been produced experimentally by injuring the adventitia by cautery¹⁸⁰ and is observed clinically in luetic aortitis. Injury to the arterial adventitia causes edema and hemorrhage in the intima; and if combined with cholesterol and thiouracil feeding in dogs, subintimal aortic atheromas are produced in regions underlying the injured adventitia.¹⁸¹ The atherosclerotic changes in the inner and medial layers of the aorta in regions underlying the areas of luetic involvement of the adventitia in all probability result similarly from interference with the circulation of tissue fluid through the aortic wall.

Certain factors aid the removal of such colloids as cholesterol from the subintimal tissue spaces of the arteries where they are prone to aggregate. Movement and massage in the arterial wall, just as in other tissues of the body, assist the flow and removal of such substances. As suggested by Wilens¹⁸² on the basis of experimental observations, the areas where lipoids accumulate permanently to form atheromas are not necessarily the same points at which they penetrate the intimal endothelial membrane from the blood stream, but rather they represent areas in which the lipoids aggregate by a process of intramural migration through the subendothelial tissue spaces of the arterial wall. The relative freedom from arteriosclerosis of muscular arteries, such as those of the diaphragm¹⁸³ and in the popliteal space,¹⁸⁴ is probably due to movement and

massage of these vessels causing lipid migration. Arterial segments which are immobilized in bony structures or confined tissues such as the intracranial arteries, or are fixed as at points of bifurcation and branching, are particularly prone to arteriosclerosis. Of interest are the observations of Westenhöffer¹⁸⁵ and Moschkowitz¹ that atherosclerotic involvement of the posterior wall of the aorta occurs earliest and is most marked opposite the prominences formed by the projecting upper and lower borders of the vertebral bodies while the regions of the aorta opposite the middle portions of the vertebrae are comparatively free of arteriosclerosis. The factor of heightened pressure during systolic impact on unyielding vascular segments undoubtedly is important as well as impairment of intramural lipid migration. A further illustration of the importance of movement and massage in preventing aggregation of lipoids is seen in the branches of the coronary arteries in the myocardium which are subjected to the constant movements and massage caused by contraction of the heart. Arteriosclerosis is infrequent in these intramural branches of the coronary arteries,³⁴ whereas the immediately contiguous main coronary arteries which lie outside the heart muscle are among the vessels most vulnerable to arteriosclerosis.

Another mechanism operates to aid in removing from the subintima lipoids which constantly enter from the bloodstream. This is phagocytosis by endothelial cells and histiocytes. Just as the other factors which contribute to the deposition and removal of colloids from the intercellular tissue fluid medium of the artery are illustrative of physiologic processes which operate in tissue fluids throughout the body, so, too, is phagocytosis of large colloidal molecules, which cannot circulate freely through tissue fluid to be removed directly via the lymphatics, a function which is not unique in the arterial wall. It does not appear reasonable to attribute any special significance to the lipid-laden macrophages, the foam cells, which are regarded by Leary³³ as

wandering from the liver and playing a primary role in the deposition of lipid in the formation of atheromas. That the occurrence of foam cells is in fact a secondary phenomenon is indicated by the studies of Duff⁶ who observed that anisotropic lipid appears extracellularly in the intima before any fat-containing cells are to be found. The observations of Hueper¹⁴ in experimental atherosclerosis caused by a variety of macromolecular colloidal carbohydrates also indicate the secondary phagocytic nature of foam cells; the colloidal carbohydrates penetrating from the blood stream into endothelial cells and also directly into the subendothelial space where they are taken up by phagocytes which are thereby transformed into foam cells. Such foam cells migrate through the wall of the artery in the intercellular ground substance and spread out between the muscle cells in the media. They aggregate in the adventitial layer around the vasa vasorum whence they are removed.

In addition to mechanical influences and phagocytosis, chemical factors probably play an important role in the disposition of colloids which enter the arterial wall. Of particular interest is the observation that the distribution of lipids in the arterial wall and in early atheromas is very similar to that in the blood,²⁰⁻²³ whereas in a more advanced stage of atheromatosis there is a greatly increased proportion of cholesterol and a decrease in the ratio of neutral fat and fatty acids.^{21,23,186,187} Neutral fats and fatty acids are much more readily removed from the intercellular medium of the vessel wall than is cholesterol,¹⁸⁸ probably being utilized in part by the tissue cells of the vascular wall. It has been suggested by Leary² that fibroblasts in the vascular wall bring about cholesterol lysis in atheroma. The fibroblasts, containing an excess of fatty acids, take up cholesterol and in these cells cholesterol esters are split, anisotropism is lost and the cholesterol is brought into solution in an excess of fatty acids; solution of cholesterol being followed by its disappearance from the lesions. Lipoid

changes effected in fibroblasts of the aorta are influenced by an agent in the blood plasma for which the name "antilipfanogen" has been proposed.¹⁸⁹ This heat-labile factor opposes the formation of fat granules in tissue cultures of aortic fibroblasts, presumably by promoting cellular utilization of fatty acids. It is reported that this factor, which is contained in Cohn's albumin "Fraction V," is decidedly low in subjects with coronary artery disease in ratio to the fat depositing lipid materials of the serum (lipfanogens).¹⁸⁹ If cholesterol lysis by fibroblasts is an important factor in the disposal of cholesterol in the vascular wall as emphasized by Leary, an explanation may be offered for the predilection of atherosclerosis in regions where the intimal cushion is thickest, an anatomic circumstance recently pointed out by Dock¹⁹⁰ to account for the frequency of atheroma in males and in the coronary arteries in particular. Where little intercellular tissue space is present in the subendothelial layer, lipoidal material aggregates in the endothelial cells and histiocytes,¹⁹¹ whereas in a thick intima with abundant intercellular space a greater amount of lipid exists free in the tissue spaces outside the cells where it undergoes precipitation.

Agencies thus exist to effect the removal of colloids from the arterial wall although these are not particularly effective for cholesterol. Arteriosclerosis in its early atheromatous stage is not an irreversible process.²⁻⁶ Small atheromatous accumulations of lipid are regularly observed in the subintimal layer of the aorta in infants which disappear with further growth.⁴ If ingestion of cholesterol is discontinued in animals in whom atheromatous changes have been produced, the lesions slowly regress and the lipid atheroma are gradually resorbed.⁶ However, the mechanisms for the removal of lipid from the arterial wall are not adequate to dispose of the lipoids constantly penetrating through the endothelial membrane. Over the span of decades increasing accumulation of lipoids occurs,^{21,71,186,187} particularly in regions

where the subintimal tissue spaces are most abundant,¹⁹⁰ with the development of arteriosclerosis in progressively increasing degree with advancing age. Such increase in concentration of lipoids leads to their precipitation, for the concentration of cholesterol in the blood stream in man is at a level not far from the point of saturation.⁹¹

AGING AND ARTERIOSCLEROSIS

There is a broad basic pattern of change in the intercellular environment common to all aging tissues. This has been studied in greatest detail in the arteries but as pointed out by Burger and Schlomka,¹⁹² and by Aschoff,¹⁵ changes similar to or identical with those in the arteries attend the process of aging in other body tissues such as the crystalline lens of the eye, cartilage, bones, tendons and muscles, the heart and its valves, veins and the supporting framework of the spleen and kidney. Basically these changes consist of an accumulation and alteration in the colloidal constituents of the intercellular fluid. The accentuation of such age changes in the artery is to be attributed to the uniqueness of the factors determining its intercellular fluid formation and circulation, i.e., the high vascular filtration pressure which greatly increases the filtration of colloids from the blood stream across the endothelial membrane. The cholesterol content of the normal aorta increases with age, the increment being accentuated in individuals with hypertension, i.e., heightened vascular filtration pressure.⁴¹

The increasing accumulation with age of protein and lipoidal substances in the intercellular medium of various tissues was known to Virchow and has been studied in specialized aspects by many investigators. A progressive increase in the deposition of collagen in the intercellular tissue medium occurs with advancing age.^{193,194} There is an accumulation of other protein-polysaccharide complexes, too, such as hyalin and mucin.¹⁹⁵ Equally significant is the progressive increase with age in the amount of lipoids such as cholesterol, fatty acids,

lecithin and neutral fat, which accumulate in the intercellular fluids by passage from the blood stream across the capillary endothelial membrane.^{71,184,196,197}

Not only do the intercellular colloids accumulate with age but they undergo important physical changes. Thus Bensley¹⁹⁸ has shown that the intercellular ground substance varies markedly with physiologic age. Originally a continuous jelly-like homogeneous substance derived from connective tissue fibroblasts, there occurs with increasing age a progressive condensation with the formation of reticular fibers which develop to form collagen and elastin. The colloidal changes with age, as Wells⁹¹ has emphasized, are similar to the changes which occur in all colloidal gels such as rubber or gelatin with aging. Cited by Wells⁹¹ and others¹⁹⁹⁻²⁰¹ as the basis of aging of protoplasm, such colloidal changes more properly apply to the intercellular fluid than to cellular protoplasm. The cellular protoplasm, just as the intercellular fluid, is in a colloidal state. The cell, however, by extracting energy from the environment is able to preserve its "orderliness," or a low state of entropy, to use Schrödinger's phrase,²⁰² and so to maintain its normal colloidal properties. With a suitable environment, as tissue culture studies have made clear, the cell is potentially immortal. The intercellular fluid on the other hand, although part and parcel of the body, is not truly a living unit and is not possessed of the vital properties necessary to maintain its functional equilibrium. The inanimate intercellular colloidal fluid is subject to the same physical deterioration with age as affects all non-living colloids. Obeying the law of all matter, with progressive increase in entropy the properties of colloids are altered and they lose their ability to bind fluids, with consequent changes in their physical characteristics. Due to loss of similar electric charges, whose repellant effect keeps colloidal particles in a finely dispersed state, their fine dispersion is diminished with aggregation into coarser granular phases, their adsorptive capacity

is decreased with a reduced ability to bind water and there is a decrease in their elasticity, permeability and chemical reactivity.⁹¹ Ultimately the colloidal gel, as it loses its colloidal properties, is transformed into a granular precipitated state. These are phenomena that may be observed in the test tube with any colloidal solution such as gelatin.

The progressive accumulation of colloids and their physical alterations with time causes a marked change in the colloidal properties of the intercellular fluid, similar to the changes which may be observed in colloids in the test tube. A precipitation of some colloidal constituents, particularly cholesterol, occurs. Under the microscope changes in the colloidal dispersion of the intercellular fluid are visible as a coarsening of the ground substance, and a granular degeneration of the collagen fiber bundles, and even more strikingly, granulation and fragmentation of the elastic fibers of the intercellular medium.^{203,204}

Such changes constitute the background of arteriosclerosis of the medial type so characteristic of aging. The elastic fibers of the arteries are, as elsewhere in the body, inanimate colloidal constituents of the intercellular tissue spaces. Quite independent of the other changes in the intercellular medium of the arteries, such as atheromatous formation, they undergo progressive degeneration with age, causing the arteries to lose their elasticity. Medial sclerosis is a distinct entity apart from atherosclerosis although it is accentuated by lipoid accumulation and degeneration. Since the nutrition of the medial musculo-elastic layer of the arteries is accomplished chiefly by penetration of nutrients directly from the blood stream through the intimal membrane and subintimal space, and only secondarily by the small vasa vasorum capillaries from the outer adventitial coat of the arteries, it is understandable that accumulation of lipoid in the subintimal space forms a mechanical barrier to the flow of nutrients to the muscle cells of the artery thereby causing degeneration. An observation of Horn and Finkel-

stein³⁴ is of interest in this regard: "Another frequent accompaniment of arteriosclerosis is medial atrophy, which appears to be directly proportional to the thickness of the adjacent (arteriosclerotic) plaque."

That impairment of nutrition to and metabolism of the cellular elements of the arteries actually occurs is indicated by the recent report of Raska,²⁰⁵ demonstrating a decrease in respiratory enzyme catalysts in arteriosclerotic aortas. Such decrease in oxidative catalysts is a general indication of impaired metabolism and can be produced experimentally in various organs by interfering with their nutrition.²⁰⁶ The decrease in respiratory catalysts in arteriosclerotic lesions may in part be due to impaired metabolic activity of the fibroblasts as well as the muscle cells. The functional capacity of fibroblasts decreases markedly with aging, as shown by Du Noüy²⁰⁷ who found the index of cicatrization, which is largely an index of fibroblastic functional activity, to be a precise measure of physiologic age. This progressive impairment is not due to inherent aging of the fibroblast cells themselves for connective tissue fragments of an old animal placed in young embryonic tissue fluid resume their full functional activities with potential immortality.²⁰⁸ Aging of the supportive tissue fibroblasts, just as aging of the parenchymal cells, is due to changes in the intercellular medium of the arteries. If, as Leary² believes, the fibroblasts in the arterial wall exert lipolytic activity, impairment of this activity with age may accentuate the development of arteriosclerotic lesions. Leary² states, "With progressing age the body gradually loses the power to remove excess cholesterol from the arteries. The lipolytic fibroblasts continue to function for some time but with little effect on advanced lesions."

SECONDARY CHANGES IN ARTERIOSCLEROSIS

The primary event in the genesis of atherosclerosis is the deposition of lipoids in the intercellular ground medium just within the endothelial membrane, with

subsequent formation of atheromatous lipoid accumulations due to mechanisms which have already been described. The further course of changes in arteriosclerosis is secondary. As suggested, interference with the circulation of tissue fluids in the vascular wall leads to impairment in the metabolic activities of the muscular media and of the fibroblast cells, decreasing their lipolytic activity. These disturbances in the functions of the cellular elements of the vessel wall are indicated by a decrease in oxidative catalysts, and anatomically by muscle atrophy, accentuating the colloidal degenerative changes in the elastic fibers of the media, i.e., medial arteriosclerosis. More important secondary changes occur in the subintima itself where the lipoids initially accumulate. These changes include the heaping up of large aggregates of lipoid in the form of plaques, precipitation of cholesterol crystals and calcium, accumulation of scavenger cells which become laden with lipoid to form foam cells in a futile attempt to remove the lipoid, these cells, together with other elements, undergoing degeneration. As elsewhere in the body where tissue injury occurs, connective tissue reaction and collagen production take place. Another change, also a characteristic reaction to tissue injury elsewhere in the body, is the growth into and around the arteriosclerotic lesions of an abundant network of small blood capillaries. Regarded thus, as a tissue reaction similar to histopathologic changes in other organs, there appears to be no necessity to invest foam cells or vasa vasorum with any special causal attributes in the genesis of arteriosclerosis. The observations of Duff⁶ indicating that anisotropic lipoid appears extracellularly in the intima before any fat-containing cells are to be found, and Hueper's similar findings with atheromatosis produced by macromolecular colloidal carbohydrates,^{13,14} indicate that foam cells are in fact a secondary phenomenon. Vascularization of atherosclerotic lesions likewise must be regarded as a secondary reactive phenomenon.^{33,34}

These secondary changes are ineffectual in accomplishing resolution of the atheromatous accumulations and indeed contribute significantly to the further evolution of arteriosclerotic lesions and their important clinical complications, i.e., narrowing or obstruction of the arterial lumen. As described by Horn and Finkelstein,³⁴ such complications may develop in several ways. These include progressive narrowing and ultimate occlusion of the lumen by large arteriosclerotic plaques, "thrombosis on a plaque" whose overlying intima is necrotic, degeneration of an arteriosclerotic plaque with rupture of the "atheromatous abscess" through the endothelium and secondary thrombus formation, intramural hemorrhage causing degenerative changes in the intima and ensuing thrombosis on the damaged endothelium, and hematoma of the arterial wall due to hemorrhage in an intramural vessel causing compression of the lumen.

These are the ultimate complications of arteriosclerosis. Unlike the early subendothelial lipid accumulations, the primary atheroma, they are irreversible changes which cannot disappear. It is obvious that arteriosclerosis in these advanced stages cannot be "cured," and that the problem of arteriosclerosis is principally one of prevention before such irreversible anatomical changes have developed.

REFERENCES

1. MOSCHKOWITZ, E. Vascular Sclerosis. New York, 1942. Oxford University Press.
2. LEARY, T. Cholesterol lysis in atheroma. *Arch. Path.*, 37: 16, 1944.
3. KUBE, N. and SSOLOWJEW, A. Über die Lipoidablagerung in der Aorta von Kindern im frühen Säuglingsalter. *Frankfurt. Ztschr. f. Path.*, 40: 302, 1930.
4. ASCHOFF, L. Lectures on Pathology. New York, 1924. Paul B. Hoeber, Inc.
5. KRISCH, H. Beitrag zur Histologie und Bedeutung der Virchowschen "fettigen Usur" der Aorta. *Virchows Arch. f. path. Anat.*, 230: 191, 1921.
6. DUFF, G. L. Nature of experimental cholesterol arteriosclerosis in rabbit. *Arch. Path.*, 22: 161, 1936. Experimental cholesterol arteriosclerosis and its relationship to human arteriosclerosis. *Arch. Path.*, 20: 81, 259, 1935.
7. GRODDECK, H. Arteriosklerose. *Ztschr. f. Altersforsch.* 1: 238, 1939.

8. LEARY, T. The genesis of atherosclerosis. *Arch. Path.*, 32: 507, 1941.
9. WINTERNITZ, M. C., THOMAS, R. M. and LE COMPTE, P. M. Studies in pathology of vascular disease. *Am. Heart J.*, 14: 399, 1937.
10. WINTERNITZ, M. C., THOMAS, R. M. and LE COMPTE, P. M. The Biology of Arteriosclerosis, Springfield, Ill., 1938. Charles C. Thomas.
11. FAHR-MANNHEIM, T. Beiträge zur experimentellen Atherosklerose unter besonderer Berücksichtigung der Frage nach dem Zusammenhang zwischen Nebennierenveränderungen und Atherosklerose. *Verhandl. d. deutsch. path. Gesellsch.*, 15: 234, 1912.
12. HIRSCH, S. L'atherome aortique des enfants. Études à propos des debuts de la soi-disant artériosclerose. *Cardiologia*, 5: 122, 1941.
13. HUEPER, W. C. Arteriosclerosis. The anoxemia theory. *Arch. Path.*, 39: 117, 1945.
14. HUEPER, W. C. The relation between etiology and morphology in degenerative and sclerosing vascular diseases. *Biol. Symposia*, 11: 1, 1945.
15. ASCHOFF, L. Introduction in Arteriosclerosis. Edited by E. V. Cowdry. New York, 1933. The Macmillan Co.
16. ANITSCHKOW, N. Zur Histophysiologie der Arterienwand. *Klin. Wchnschr.*, 4: 2233, 1925.
17. ANITSCHKOW, N. Das Wesen und die Entstehung der Atherosklerose. *Ergeb. d. inn. Med. u. Kinderh.*, 28: 1, 1925.
18. ANITSCHKOW, N. Experimental Arteriosclerosis in Animals. Chapt. 10 in Arteriosclerosis. Edited by E. V. Cowdry. New York, 1933. The Macmillan Co.
19. BRUGER, M. and POINDEXTER, C. A. Relation of plasma cholesterol to obesity and to some of the complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis). *Arch. Int. Med.*, 53: 423, 1934.
20. WEINHOUSE, S. and HIRSCH, E. F. Atherosclerosis; lipids of serum and tissues in experimental atherosclerosis of rabbits. *Arch. Path.*, 30: 856, 1940.
21. HIRSCH, E. F. and WEINHOUSE, S. Role of lipids in atherosclerosis. *Physiol. Rev.*, 23: 185, 1943.
22. PAGE, I. H. Some aspects of nature of chemical changes occurring in atheromatosis. *Ann. Int. Med.*, 14: 1741, 1941.
23. MCARTHUR, C. S. The acetone-soluble lipid of the atheromatous aorta. *Biochem. J.*, 36: 559, 1942.
24. GIBBS, C. B. F., BUCKNER, E. and BLOOR, W. R. Cholesterol to cholesterol ester ratio in plasma of diabetics with advanced arteriosclerosis. *New England J. Med.*, 209: 384, 1933.
25. WHITE, P. Diabetes in children. *Bull. New York Acad. Med.*, 10: 347, 1934.
26. RABINOWITZ, I. M. Arteriosclerosis in diabetes; relationship between plasma cholesterol and arteriosclerosis; effects of high carbohydrate, low calorie diet. *Ann. Int. Med.*, 8: 1436, 1935.
27. LISA, J. R., MAGIDAY, M., GALLOWAY, I. and HART, J. F. Arteriosclerosis with diabetes mellitus; study of pathologic findings in 193 diabetic and 2,250 non-diabetic patients. *J. A. M. A.*, 120: 192, 1942.
28. RIEBOLD, G. Dauernde erhebliche Blutdrucksteig-

- erung als Frühsymptom einer Gehirnarteriosklerose. *München. med. Wchnschr.*, 64: 1390, 1917.
29. SIGLER, L. H. Spontaneous nonrhythmic variations in blood pressure levels and in "silent gap"; theory of vasomotor arrhythmia. *Am. J. M. Sc.*, 177: 494, 1929.
 30. RAAB, W. Hirnblutuntersuchungen bei Hypertonie. *Ztschr. f. klin. Med.*, 115: 577, 1931.
 31. BORDLEY, J., III and BAKER, B. M., JR. Arteriosclerosis of cerebral vessels and pathogenesis of hypertension. *Bull. Johns Hopkins Hosp.*, 39: 229, 1926.
 32. KATZ, L. N. and DAUBER, D. V. Pathogenesis of atherosclerosis. *J. Mt. Sinai Hosp.*, 12: 382, 1945.
 33. LEARY, T. Vascularization of atherosclerotic lesions. *Am. Heart J.*, 16: 549, 1938.
 34. HORN, H. and FINKELSTEIN, L. E. Arteriosclerosis of coronary arteries and mechanism of their occlusion. *Am. Heart J.*, 19: 655, 1940.
 35. ALTSCHUL, R. Histologic analysis of arteriosclerosis. *Arch. Path.*, 38: 305, 1944.
 36. RAMSAY, E. M. Studies in pathology of vascular disease; nutrition of blood vessel wall: review of literature. *Tale. J. Biol. & Med.*, 9: 43, 1936.
 37. PETROFF, J. R. Über die Vitalfärbung der Gefäßwandungen. *Beitr. z. path. Anat.*, 71: 115, 1922–1923.
 38. LANGE, F. Studien zur Pathologie der Arterien, insbesondere zur Lehre von der Arteriosklerose. *Virchows Arch. f. path. Anat.*, 248: 463, 1924.
 39. IWANOV, G. Die lymphgefäße der Wände der Blutgefäße—Vasa lymphatica vasorum sanguinorum (zur Methodik ihrer Injektion). *Ztschr. f. Anat. u. Entwicklungsgesch.*, 99: 669, 1933.
 40. WOLKOFF, K. and HESSE, E.¹⁶
 41. FABER, M. The cholesterol content of the human aorta in relation to the serum cholesterol concentration. *Acta med. Scandinav.*, 125: 418, 1946.
 42. HUNTER, A. Blood pressure among standard lives. *J. Inst. Actuaries*, 70: 60, 1939.
 43. DALEY, R. M., UNGERLEIDER, H. E. and GUBNER, R. S. Prognosis in hypertension. *J. A. M. A.*, 121: 383, 1943.
 44. ANREP, G. V., DAVIS, J. C. and VOLHARD, E. Effect of pulse pressure upon coronary blood flow. *J. Physiol.*, 73: 405, 1931.
 45. GREGG, D. E. The phasic variations in coronary flow, studied by autoperfusion method. *Proc. Am. Physiol. Soc.*, 46th Annual Meet., New York, March 28–31, 1934. *Am. J. Physiol.*, 109: 44, 1934.
 46. JOHNSON, J. R. and DI PALMA, J. R. Intramyocardial pressure and its relation to aortic blood pressure. *Am. J. Physiol.*, 125: 234, 1939.
 47. GREGG, D. E. Phasic changes in flow through different coronary branches. Chapter in *Blood, Heart and Circulation*. *Am. Assoc. Adv. Sc.*, 81, 1940.
 48. EHRLICH, W., DE LA CHAPELLE, C. E. and COHN, A. E. Anatomical ontogeny; man; study of coronary arteries. *Am. J. Anat.*, 49: 241, 1931.
 49. DAVSON, H. and DANIELLI, J. F. *The Permeability of Natural Membranes*. New York, 1943. The Macmillan Co.
 50. CHAMBERS, R. and ZWEIFACH, B. W. Capillary endothelial cement in relation to permeability. *J. Cell. & Comp. Physiol.*, 15: 255, 1940.
 51. LANGE, K. Capillary permeability in myxedema. *Am. J. M. Sc.*, 208: 5, 1944.
 52. SHAPIRO, S. Relation of certain glands of internal secretion to development of atherosclerosis. *Endocrinology*, 11: 279, 1927.
 53. Influence of thyroidectomy, splenectomy, gonadectomy, and suprarenalectomy upon the development of experimental atherosclerosis in rabbits. *J. Exper. Med.*, 45: 595, 1927.
 54. STEINER, A. and KENDALL, F. E. Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil. *Arch. Path.*, 42: 433, 1946.
 55. MURATA, M. and KATAOKA, S. Experimentelle Arteriosklerose und Schilddrüsenfütterung. *Verhandl. d. Jap. path. Gesellsch.*, 8: 221, 1918.
 56. LIEBIG, H. Die Beeinflussung der experimentellen Atherosklerose durch Jodbehandlung. *Arch. f. exper. Path. u. Pharmacol.*, 159: 265, 1931.
 57. TURNER, K. B. and KHAYAT, G. B. Studies on prevention of cholesterol atherosclerosis in rabbits; influence of thyroidectomy upon protective action of potassium iodide. *J. Exper. Med.*, 58: 127, 1933.
 58. FRIEDLAND, I. B. Untersuchungen über den Einfluss der Schilddrüsenpräparate auf die experimentelle Hypercholesterinämie und Atherosklerose. *Ztschr. f. d. ges. exper. Med.*, 87: 683, 1933.
 59. TURNER, K. B. Studies on prevention of cholesterol atherosclerosis in rabbits; effects of whole thyroid and of potassium iodide. *J. Exper. Med.*, 58: 115, 1933.
 60. PAGE, I. H. and BERNHARD, W. G. Cholesterol-induced atherosclerosis; its prevention in rabbits by feeding of organic iodine compound. *Arch. Path.*, 19: 530, 1935.
 61. MALISOFF, W. M. Prevention of atherosclerosis in rabbits; administration of potassium thiocyanate. *Proc. Soc. Exper. Biol. & Med.*, 35: 356, 1936.
 62. HUEPER, W. C. Experimental studies on the therapy and prevention of degenerative vascular diseases. 1. The effects of medication with potassium thiocyanate on experimental cholesterol atheromatosis. *Arch. Path.*, 38: 93, 1944.
 63. MEEKER, D. R., KESTEN, H. D. and JOBLING, J. W. Effect of iodine on cholesterol-induced atherosclerosis. *Arch. Path.*, 20: 337, 1935.
 64. DAVIS, D., STERN, B. and LESNICK, G. Lipid and cholesterol content of blood of patients with angina pectoris and arteriosclerosis. *Ann. Int. Med.*, 11: 354, 1937.
 65. STEINER, A. and DOMANSKI, B. Serum cholesterol level in coronary arteriosclerosis. *Arch. Int. Med.*, 71: 397, 1943.
 66. LANDÉ, K. E. and SPERRY, W. M. Human atherosclerosis in relation to cholesterol content of blood serum. *Arch. Path.*, 22: 301, 1936.
 67. MORRISON, L. M., HALL, L. and CHENEY, A. L. Cholesterol metabolism: blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis. *Am. J. M. Sc.*, 216: 32, 1948.
 68. LERMAN, J. and WHITE, P. D. Metabolic changes in young people with coronary heart disease. *J. Clin. Investigation*, 25: 914, 1946.

68. UNDERDAHL, L. O. and SMITH, H. L. Coronary artery disease in women under the age of forty. *Proc. Staff Meet., Mayo Clin.*, 22: 479, 1947.
69. DOCK, W. Personal communication.
70. KUCZYNSKI, B. Pathologisch-geographische Untersuchungen in der kirgisch-ungarischen Steppe. *Klin. Wchschr.*, 4: 39, 1925.
71. ROSENTHAL, S. R. Studies in atherosclerosis: chemical, experimental and morphologic; rôles of cholesterol metabolism, blood pressure and structure of aorta; fat angle of aorta (F. A. A.) and infiltration-expression theory of lipid deposit. *Arch. Path.*, 18: 473, 660, 1934. Studies in atherosclerosis: chemical, experimental and morphologic; possible dangers of iodine therapy in atherosclerosis of aorta seen from experimental standpoint. *Arch. Path.*, 18: 827, 1934.
72. DILLON, J. A. and EVANS, L. R. Primary amyloidosis; report of 3 cases. *Ann. Int. Med.*, 17: 722, 1942.
73. LEUPOLD, E. Untersuchungen über die Mikrochemie und Genese des Amyloids. *Beitr. z. path. Anat. u. z. allg. Path.*, 64: 347, 1917.
74. NAKONETSCHNY, A. Über die pathologischen Arterienveränderungen in der Milz. *Virchows Arch. f. path. Anat.*, 245: 564, 1923.
75. HUEPER, W. C. and ICHNIOWSKI, C. T. Toxicopathologic studies on dye T-1824. *Arch. Surg.*, 48: 17, 1944.
76. ZETTLER, L. Die Wirkung von Gefäßmitteln auf die Permeabilität der Arterien. *Arch. f. exper. Path. u. Pharmacol.*, 185: 141, 1937.
77. PETROFF, J. R. Über die Vitalfärbung der Gefäßwandungen. *Beitr. z. path. Anat.*, 71: 115, 1922–1923.
78. OKUNEFF, N. Vital dye imbibition of aorta wall. *Virchows Arch. f. path. Anat.*, 269: 685, 1926.
79. BRUGER, M. State of cholesterol and nature of cholesterol-protein complex in pathological body fluids. *J. Biol. Chem.*, 108: 463, 1935.
80. MORETON, J. R. Atherosclerosis and alimentary hyperlipemia. *Science*, 106: 190, 1947.
81. SCHÖNHOLZER, G. Zur Frage des cholesterolytischen Vermögens des Blutserums. *Helvet. med. acta*, 6: 692, 1939.
82. BLIX, G., TISELIUS, A. and SVENSSON, H. Lipids and polysaccharides in electrophoretically separated blood serum proteins. *J. Biol. Chem.*, 137: 485, 1941.
83. WENT, S. and GORECZKY, L. Die Verteilung der Serumphosphatide und des Cholesterins in durch Filtration durch grossporige Kollodiumfilter gewonnenen Serumultrafiltraten. *Biochem. Ztschr.*, 239: 441, 1931.
84. MAN, E. B. and PETERS, J. P. Permeability of capillaries to plasma lipoids. *J. Clin. Investigation*, 12: 1031, 1933.
85. BRUGER, M. The lipiduria of Bright's disease: observations on the urinary excretion of cholesterol, lipid phosphorus and fatty acids. *J. Clin. Investigation*, 15: 464, 1936.
86. BING, J. and STARUP, U. Investigations on hyperlipaemia and cholesterinuria. *Acta med. Scandinav.*, 86: 12, 1935.
87. FISHBERG, A. M. Hypertension and Nephritis. P. 384, 4th ed. Philadelphia, 1939. Lea & Febiger.
88. KUJATH, G. Zur Frage der differential-diagnostischen Bedeutung des Liquor-cholesterins. *Allg. Ztschr. f. Psychiat.*, 121: 249, 1943.
89. DECKWITZ, R. Cholesterin und Lecithin im Wasser- und Säure-Basenhaushalt. *Klin. Wchschr.*, 9: 2336, 1930.
90. COOK, R. P. Cholesterol metabolism. *Nutrition Abstr. & Rev.*, 12: 1, 1942.
91. WELLS, H. G. The Chemistry of Arteriosclerosis. Chapter 11 in Arteriosclerosis. Edited by E. V. Cowdry. New York, 1933. The Macmillan Co.
92. LOEPER, M., LEMAIRE, A. and LESURE, A. Le pouvoir cholestérololytique du sérum humain normal et pathologique. *Compt. rend. Soc. de biol.*, 98: 101, 1928.
93. ECK, M. and DESBORDES, J. Influence de l'âge sur les variations de la cholestérinémie et du pouvoir cholestérololytique. *Compt. rend. Soc. de biol.*, 118: 498, 1935. Sur le taux de la cholestérine et la pouvoir cholestérololytique du sérum de vieillard. *Compt. rend. Soc. de biol.*, 117: 428, 1934.
94. ALVAREZ, C. and NEUSCHLOSZ, S. M. Untersuchungen über das Blutcholesterin bei arteriellen Hochdruck. *Klin. Wchschr.*, 10: 244, 1931.
95. LONGSWORTH, L. G., SHEDLOVSKY, T. and MAC-INNES, D. A. Electrophoretic patterns of normal and pathological human blood serum and plasma. *J. Exper. Med.*, 70: 399, 1939.
96. BLOCH, K. and RITTENBERG, D. On the utilization of acetic acid for cholesterol formation. *J. Biol. Chem.*, 145: 625, 1942.
97. RITTENBERG, D. The William Henry Welch lectures. The application of isotope technique to problems of biology and medicine. *J. Mt. Sinai Hosp.*, 14: 891, 1947–1948.
98. BLOCH, K., BERG, B. N. and RITTENBERG, D. Biological conversion of cholesterol to cholic acid. *J. Biol. Chem.*, 149: 511, 1943.
99. SOBOTKA, H. Physiological Chemistry of the Bile. Baltimore, 1937. Williams and Wilkins.
100. WRIGHT, A. Cholesterol and cholesterol esters in dog bile; quantitative methods. *J. Exper. Med.*, 59: 407, 1934.
101. SCHRAMM, G. and WOLFF, A. Über die Cholesterinesterasen und ihre Beziehungen zur Fettresorption und zum Fetttransport. *Ztschr. f. physiol. Chem.*, 263: 61, 1940. Über die enzymatische Veresterung einige Steroide. *ibid.* 263: 73, 1940. Cited by Weinhouse, S. in Blood Cholesterol. *Arch. Path.*, 35: 438, 1943.
102. BLOOR, W. R. Biochemistry of the Fatty Acids. New York, 1943. Reinhold Publishing Corp.
103. MEMBER, S., BRUGER, M. and OPPENHEIM, E. Experimental atherosclerosis; effects of various bile acids on cholesterol levels. *Arch. Path.*, 38: 210, 1944.
104. COOK, R. P. Cholesterol feeding and fat metabolism. *Biochem. J.*, 30: 1630, 1936.
105. ARTOM, C., SARZANA, G., PERRIER, C., SANTANGELO, M. and SEGRÉ, E. Synthèse des phospholipides au cours de l'absorption des graisses. *Arch. internat. de physiol.*, 45: 32, 1937.
106. FRIES, B. A., RUBEN, S., PERLMAN, I. and CHAIKOFF, I. L. Radioactive phosphorus as indicator of phospholipid metabolism; role of stomach, small intestine, and large intestine in phospholipid

- metabolism in presence and absence of ingested fat. *J. Biol. Chem.*, 123: 587, 1938.
107. VERZAR, F. and LASZT, L. Hemmung der Fettresorption durch Monojodessigsäure und Phloerhizin. *Biochem. Ztschr.*, 270: 35, 1934.
 108. SINCLAIR, R. G. Blood phospholipid as transport mechanism. *J. Biol. Chem.*, 115: 211, 1936.
 109. PETERS, J. P. and VAN SLYKE, D. D. Quantitative Clinical Chemistry. Vol. 1. Interpretations, 2nd ed. Baltimore, 1946. Williams and Wilkins.
 110. BALLOU, G. A., BOYER, P. D. and LUCK, J. M. Electrophoretic mobility of human serum albumin as affected by lower fatty acid salts. *J. Biol. Chem.*, 159: 111, 1945.
 111. LUETSCHER, J. A., JR. Electrophoretic analysis of plasma and urinary proteins. *J. Clin. Investigation*, 19: 313, 1940.
 112. LEWIS, L. A. and McCULLAGH, E. P. Electrophoretic analysis of plasma proteins in hyperthyroidism and hypothyroidism. *Am. J. M. Sc.*, 208: 727, 1944.
 113. CHARGAFF, E., ZIFF, M. and MOORE, D. H. Studies on chemistry of blood coagulation; electrophoretic study of effect of anticoagulants on human plasma complement. *J. Biol. Chem.*, 139: 383, 1941.
 114. HAHN, P. F. Abolishment of alimentary lipema following injection of heparin. *Science*, 98: 19, 1943.
 115. BOXER, G. E. and STETTEN, DEW., JR. Effect of dietary choline upon rate of turnover of phosphatide choline. *J. Biol. Chem.*, 153: 617, 1944.
 116. FORBES, J. C. Effect of thyroxine on neutral fat and cholesterol content of body and liver of rats. *Endocrinology*, 35: 126, 1944.
 117. KARTIN, B. L., MAN, E. B., WINKLER, A. W. and PETERS, J. P. Blood ketones and serum lipids in starvation and water deprivation. *J. Clin. Investigation*, 23: 824, 1944.
 118. KESTEN, H. D. and SILBOWITZ, R. Experimental atherosclerosis and soya lecithin. *Proc. Soc. Exper. Biol. & Med.*, 49: 71, 1942.
 119. ADLERSBERG, D. and SOBOTKA, H. Effect of prolonged lecithin feeding on hypercholesterolemia. *J. Mt. Sinai Hosp.*, 9: 955, 1943.
 120. HERRMANN, G. R. Cholesterol levels in various diseases and effects of decholesterizing agents. *Texas State J. Med.*, 42: 260, 1946.
 121. STEINER, A. and DOMANSKI, B. Effect of feeding of "soya lecithin" on serum cholesterol level of man. *Proc. Soc. Exper. Biol. & Med.*, 55: 236, 1944.
 122. BÜRGER, M. and WINTERSEEL, W. Sterinausscheidung und Sterinbalanz bei totalem Gallengangsverschluss. *Ztschr. f. d. ges. exper. Med.*, 66: 459, 1929; cited by Weinhouse, S.: Blood Cholesterol. *Arch. Path.*, 35: 438, 1943.
 123. FLEISCHMANN, W. and SHUMACKER, H. B., JR. The relationship between serum cholesterol and total body cholesterol in experimental hyper- and hypothyroidism. *Bull. Johns Hopkins Hosp.*, 71: 175, 1942.
 124. BOYD, E. M. Lipid content of white blood cells in normal young women. *J. Biol. Chem.*, 101: 623, 1933.
 125. BOYD, E. M. Reaction of lipids in blood leucocytes to fever and infection. *Surg., Gynec. & Obst.*, 60: 205, 1935.
 126. OKEY, R. Middle and old age in cholesterol-fed rats. *Proc. Soc. Exper. Biol. & Med.*, 46: 466, 1941.
 127. OKEY, R. and BOYDEN, R. E. Studies of metabolism of women; variations of lipid content of blood in relation to menstrual cycle. *J. Biol. Chem.*, 72: 261, 1927.
 128. BUNTING, C. H. and HUSTON, J. Fate of the lymphocyte. *J. Exper. Med.*, 33: 593, 1921.
 129. SCHOENHEIMER, R. Über eine Störung der Cholesterin ausscheidung. (Ein Beitrag zur Kenntnis der Hypercholesterinämien). *Ztschr. f. klin. Med.*, 123: 749, 1933.
 130. RUZICKA, L. and PRELOG, V. Isolation of cholesterol from pig testes. *Helvet. Chim. Acta*, 26: 975, 1943. Isolation of cholesterol from pig spleen. *Helvet. chim. acta*, 26: 2222, 1943.
 131. GILMAN, A. The effects of drugs on nerve activity. *Ann. New York Acad. Sc.*, 47: 549, 1946.
 132. ANNEGERS, J. H., SNAPP, F. E., IVY, A. C. and ATKINSON, A. J. Effect of cinchophen on secretion of cholic acid. *Arch. Int. Med.*, 73: 1, 1944.
 133. ASKANAZY, S. Rhodan-Kalzium-Diuretin gegen Hypertonie. *München med. Wchnschr.*, 74: 1793, 1927.
 134. LINDBERG, H. A., WALD, M. H. and BARKER, M. H. Observations on pathologic effects of thiocyanate; experimental study. *Am. Heart J.*, 21: 605, 1941.
 135. WESTPHAL, K. and BLUM, R. Die Rhodentherapie des genuinen arteriellen Hochdrucks und ihre theoretische Begründung. *Deutsches Arch. f. klin. Med.*, 152: 331, 1926.
 136. HUEBEL, W. C. Experimental studies on the therapy and prevention of degenerative vascular diseases. 1. The effects of medication with potassium thiocyanate on experimental cholesterol atheromatosis. *Arch. Path.*, 38: 93, 1944.
 137. GOEBEL, F. Sur l'influence du système végétatif sur la teneur du sang en cholestérine. *J. de physiol. et de path. gén.*, 30: 340, 1932.
 138. HILL, E. and KOEHLER, A. E. Effect of epinephrine on lipid excretion. *J. Biol. Chem.*, 98: 185, 1932.
 139. ASHE, B. I. and BRUGER, M. Cholesterol content of plasma in chronic nephritis and retention uremia. *Am. J. M. Sc.*, 186: 670, 1933.
 140. BRUGER, M. and POINDENTER, C. A. Effect of ingestion of water and of urea on cholesterol content of plasma. *J. Biol. Chem.*, 101: 21, 1933.
 141. MAYER, A. and SCHAEFFER, G. Variations de la teneur des tissus en lipoides et en eau au cours de l' inanition absolue. *J. de physiol. et de path. gén.*, 16: 203, 1914-1915.
 142. KOUNTZ, W. B., SONNENBERG, A., HOFSTATTER, L. and WOLFF, G. Blood cholesterol levels in elderly patients. 1. Relation of age, sex, basal metabolic rate, cardiac decompensation, and Coronary and peripheral sclerosis to blood cholesterol levels in the aged. *Biol. Symposia*, 11: 79, 1945.
 143. HEYMANN, W. and RACK, F. Independence of serum cholesterol from exogenous cholesterol in infants and children. *Am. J. Dis. Child.*, 65: 235, 1943.
 144. GOUGH, N. Effect of diet on concentration of cho-

- lesterol in blood and bile. *Brit. M. J.*, 2: 390, 1943.
145. COOK, R. P. Cholesterol feeding and fat metabolism. *Biochem. J.*, 30: 1630, 1936.
 146. ECKSTEIN, H. C. Sterol metabolism in young white rats; effect of saponifiable lipids and degree of unsaturation of lipids on sterol metabolism of white rat. *J. Biol. Chem.*, 125: 99, 1938. Sterol metabolism in young white rats; effect of high and low fat diets on sterol balances and sterol content of hair of young white rats. *J. Biol. Chem.*, 125: 107, 1938.
 147. PAPENKORT, E. Über den Einfluss der Fettbelastung auf Resorption und Ausscheidung der Gallensäuren beim Menschen. *Ztschr. f. d. ges. exper. Med.*, 93: 249, 1934.
 148. KEMPNER, W. Some effects of rice diet treatment of kidney disease and hypertension. *Bull. New York Acad. Med.*, 22: 358, 1946.
 149. GARDNER, J. A. and GAINSBOROUGH, H. Blood cholesterol studies in biliary and hepatic disease. *Quart. J. Med.*, 23: 465, 1930.
 150. GARDNER, J. A., GAINSBOROUGH, H. and MURRAY, R. M. Distribution of sterols in human faeces; examination of ileal contents. *Biochem. J.*, 29: 1139, 1935.
 151. SPERRY, W. M. Lipid excretion: study of relationship of bile to fecal lipids with special reference to certain problems of sterol metabolism. *J. Biol. Chem.*, 71: 351, 1927.
 152. BEUMER, H. and HEPNER, F. Über die Ausscheidungswege des Cholesterins. *Ztschr. f. d. ges. exper. Med.*, 64: 787, 1929.
 153. ROFFO, A. H. Descolesterinización por el Alcaucil (*Cynara Scolymus*). *Bol. Inst. de med. exper. para el estud. y trat. de cáncer*, 20: 65, 1943.
 154. ROFFO, A. H. Egg-plant (*Solanum melongena* L.) in decholesterolization. *Vale J. Biol. & Med.*, 18: 25, 1945.
 155. SNELL, A. M. Tropical and nontropical sprue (chronic idiopathic steatorrhea): their probable interrelationship. *Ann. Int. Med.*, 12: 1632, 1939.
 156. ROY, A. and SEN, P. B. Effect of quinine on absorption of fat. *Ann. Biochem. & Exper. Med.*, 3: 9, 1943.
 157. FRAZER, A. C. Lipolysis and fat absorption. *J. Physiol.*, 102: 329, 1943.
 158. BURR, G. O. and BARNES, R. H. Non-caloric functions of dietary fats. *Physiol. Rev.*, 23: 256, 1943.
 159. CURTIS, A. C. and KLINE, E. M. Influence of liquid petrolatum on blood content of carotene in human beings. *Arch. Int. Med.*, 63: 54, 1939.
 160. DAM, H. Formation of coprosterol in intestine: action of intestinal bacteria on cholesterol. *Biochem. J.*, 28: 820, 1934.
 161. DUBOS, R. J. Personal communication.
 162. ROSENHEIM, O. and WEBSTER, T. A. Mechanism of coprosterol in vivo; its inhibition by succinyl sulphathiazole and by carbarsone. *Biochem. J.*, 37: 580, 1943.
 163. ANCHEL, M. and SCHOENHEIMER, R. Deuterium as indicator in study of intermediary metabolism; further studies in coprosterol formation. Use of compounds containing labile deuterium for biological experiments. *J. Biol. Chem.*, 125: 23, 1938.
 164. SCHMIDT, L. H. and HUGHES, H. B. Studies on bile acid metabolism; fate of cholic acid in guinea pig. *J. Biol. Chem.*, 143: 771, 1942.
 165. SCHMIDT, L. H., HUGHES, H. B., GREEN, M. H. and COOPER, E. Studies on bile acid metabolism; action of *Alcaligenes faecalis* on cholic acid. *J. Biol. Chem.*, 145: 229, 1942.
 166. HUGHES, H. B. and SCHMIDT, L. H. Oxidation of steroids by *Alcaligenes faecalis*. *Proc. Soc. Exper. Biol. & Med.*, 51: 162, 1942.
 167. HOEHN, W. M., SCHMIDT, L. H. and HUGHES, H. B. Studies on bile acid metabolism; separation and identification of ketocholanic acids formed during oxidation of cholic acid by *Alcaligenes faecalis*. *J. Biol. Chem.*, 152: 59, 1944.
 168. SCHMIDT, L. H. and HUGHES, H. B. Conversion of hydroxy-steroids to keto-steroids. *U. S. P.* 2: 360, 447, 1944. Cited by Turfitt, G. E. Microbiological agencies in the degradation of steroids. II. Steroid utilization by the microflora of soils. *J. Bact.*, 54: 557, 1947.
 169. SCHOENHEIMER, R., RITTENBERG, D., and GRAFF, M. Deuterium as indicator in study of intermediary metabolism; mechanism of coprosterol formation. *J. Biol. Chem.*, 111: 183, 1935.
 170. HERTER, C. A. and KENDALL, A. I. Influence of dietary alternations on the types of intestinal flora. *J. Biol. Chem.*, 7: 203, 1909-1910.
 171. WOLLSTEIN, M. Influence of high protein feeding on the general metabolism, on the intestinal flora and on the body temperature of infants. Part 3. Bacteriological observations. *Am. J. Dis. Child.*, 4: 279, 1912.
 172. TORREY, J. C. Regulation of the intestinal flora of dogs through diet. *J. M. Res.*, 39: 415, 1918-1919.
 173. ROSENHEIM, O. and WEBSTER, T. A. Dietary factor concerned in coprosterol formation. *Biochem. J.*, 35: 920, 1941.
 174. ROSENHEIM, O. and WEBSTER, T. A. Mechanism of coprosterol formation in vivo; cholestenone as intermediate. *Biochem. J.*, 37: 513, 1943.
 175. ROSENHEIM, O. and STARLING, W. W. Oxycholesterol. *Chem. Ind.*, 52: 1056, 1933.
 176. SOBOTKA, H. Chemistry of Steroids. Baltimore, 1938. Williams & Wilkins Co.
 177. DIELS, O. and ABDERHALDEN, E. Zur Kenntniss des Cholesterins. *Ber. d. deutsch. chem. Gesellsch.*, 37: 3092, 1904.
 178. SCHOENHEIMER, R. and EVANS, E. A., JR. Allocholesterol and epiallocholesterol. *J. Biol. Chem.*, 114: 567, 1936.
 179. WOLKOFF, K. Zur Frage der Morphologie der Lipoidablagerungen im Organismus der Teermäuse bei verschiedener Nahrungsart. *Ztschr. f. Krebsforsch.*, 31: 291, 1930.
 180. SOLOWJEW, A. Experimentelle Untersuchungen über die Bedeutung von lokaler Schädigung für die Lipoidablagerung in der Arterienwand. *Ztschr. f. d. ges. exper. Med.*, 69: 94, 1929-1930.
 181. SCHLICHTER, J. G. Vascularization of the aorta in different species in health and disease. Am. Soc. Study of Arteriosclerosis, 2nd meet., Chicago, November 2, 1947. *Am. Heart J.*, 35: 850, 1948.
 182. WILENS, S. L. Distribution of intimal atheromatous lesions in arteries of rabbits on high cholesterol diets. *Am. J. Path.*, 18: 63, 1942.

183. WARTMAN, W. B. Incidence and severity of arteriosclerosis in organs from 500 autopsies. *Am. J. M. Sc.*, 186: 27, 1933.
184. PAGE, I. H. Arteriosclerosis and lipid metabolism. *Biol. Symposia*, 11: 43, 1946.
185. WESTENHÖFER, P. Über die Lokalisation und phylogenetische Grundlage der Verfettungen und Sklerosen der Aorta und ihre Aeste. *Deutsche med. Wchnschr.*, 48: 518, 1922.
186. MEEKER, D. R. and JOBLING, J. W. Chemical study of arteriosclerotic lesions in human aorta. *Arch. Path.*, 18: 252, 1934.
187. SCHÖNHEIMER, R. Zur Chemie der gesunden und der atherosklerotischen Aorta. Ueber die quantitativen Verhältnisse des Cholesterins und der Cholesterinester. *Ztschr. f. physiol. Chem.*, 160: 61, 1926.
188. CHRISTIANSON, O. O. Observations on lesions produced in arteries of dogs by injection of lipids; lipids injected: human fat, fatty acids, soaps and cholesterol. *Arch. Path.*, 27: 1011, 1939.
189. SIMMS, H. S., PARSHLEY, M. S. and PITT, R. B. Fat deposition in vitro caused by lipfanogens and opposed by antilipfanogen. *J. Gerontol.*, 2: 205, 1947.
190. SIMMS, H. S., PARSHLEY, M. S., PITT, R. B. and FULTON, J. B. Further studies on the fat-depositing mechanism. *Am. Heart J.*, 36: 469, 1948.
190. DOCK, W. Predilection of atherosclerosis for coronary arteries. *J. A. M. A.*, 131: 875, 1946.
191. ZINSERLING, W. D. Cited by Hueper, W. C. in Arteriosclerosis. The anoxemia theory. *Arch. Path.*, 39: 187, 1945.
192. BÜRGER, M. and SCHLOMKA, G. Ergebnisse und Bedeutung chemischer Gewebsuntersuchungen für die Altersforschung. *Klin. Wchnschr.*, 7: 1944, 1928.
193. TROITZKAJA-ANDREEWA, A. M. Zur Kenntnis der Altersveränderungen der Arterien. (Über die Altersfibrose der Arterienwand.) *Frankfurt. Ztschr. f. Path.*, 41: 120, 1931.
194. WETZEL, G. Altersanatomie. *Verhandl. d. anat. Gesellsch.*, 41: 15, 1932.
195. HERXHEIMER, G. Ueber das Verhalten der kleinen Gefäße der Milz. *Berl. klin. Wchnschr.*, 54: 82, 1917.
196. BALDAUF, L. K. Chemistry of atheroma and calcification (Aorta). *J. M. Res.*, 15: 355, 1906.
197. SCHÖNHEIMER, R. Zur Chemie der gesunden und der atherosklerotischen Aorta. Ueber die quantitativen Verhältnisse des Cholesterins und der Cholesterinester. *Ztschr. f. physiol. Chem.*, 160: 61, 1926.
198. BENSLEY, S. H. On presence, properties and distribution of intercellular ground substance of loose connective tissue. *Anat. Rev.*, 60: 93, 1934.
199. ROCOSOLANO, A. DE G. A physico-chemical hypothesis of aging. *Kolloidchem. Beihefte*, 19: 441, 1924.
200. RUZICKA, V. Beiträge zum Studium der Protoplasmahysteresis und der hysteretischen Vorgänge. (Zur Kausalität des Alterns.) *Arch. f. mikr. Anat. u. Entwickl.*, 101: 459, 1924.
201. DHAR, N. R. Senescence inherent property of animal cells. *Quart. Rev. Biol.*, 7: 68, 1932.
202. SCHRÖDINGER, E. What is Life? New York, 1946. The Macmillan Co.
203. WEIDMAN, F. Aging of the skin, in Problems of Aging, ed. by E. V. Cowdry. Baltimore, 1939. Williams & Wilkins Co.
204. EJIRI, I. Histology of human skin: II. On differences in the elastic fibers of the skin according to sex and age. *Japan J. Dermat. & Urol.*, 40: 216, 1936; abstracted, *Arch. Dermat. & Syph.*, 37: 664, 1938.
205. RASKA, S. B. Discussion in Experimental Hypertension, A Symposium. *New York Academy Sc. Special publication*. 3: 50, 1946.
206. RASKA, S. B. Metabolism of kidney in experimental renal hypertension; concentration of cytochrome c and activities of cytochrome oxidase and of succinic dehydrogenase systems in kidney of dogs with experimental renal hypertension. Inhibitory effect of renin and of kidney tissue preparations from hypertensive dogs on respiratory enzymes. *J. Exper. Med.*, 82: 227, 1945.
207. DU NOUY, P. L. Biological Time. New York, 1937. The Macmillan Co.
208. CARREL, A. The relation of cells to one another. Chap. 9 in Human Biology and Racial Welfare. Ed. by E. V. Cowdry. New York, 1930. Paul B. Hoeber, Inc.

Seminars on Congestive Failure

The Mechanism of Heart Failure^{*}

A Resume of Physiologic Factors in Cardiovascular Failure

ROBERT PAINE, M.D.† AND JOHN R. SMITH, M.D.

St. Louis, Missouri

WITHIN recent years many informative observations concerning the mechanism of cardiac failure have been added to the record. A number of these studies entailed animal experiments from which indirect though valuable data regarding heart disease in man may be derived. Many of the recent studies included observations of cardiac performance in normal individuals and in patients with heart disease. In the latter instances technical refinements were utilized permitting the observation of certain intracardiac and intravascular pressure relationships and an accurate determination of cardiac output. Although the pathologic physiology of heart failure has been widely investigated, the employment of newer methods in the study of cardiovascular physiology in man has recreated a lively interest in the problem. At present new ideas are advanced in rapid succession and many older concepts are being revised. It may be of some value to re-examine the question of the genesis of cardiac failure in the light of valuable evidence from clinical and experimental observations now at hand.

MYOCARDIAL INJURY

It is quite admissible that failure of the heart arises in consequence of primary injury

to the myocardium. The association of clinical heart failure with coronary disease, hypertrophy of the muscle fibers and other morphologic changes of acquired and congenital lesions is so familiar that further comment is unnecessary. However, the means by which myocardial damage invokes failure of the organ is poorly understood.³⁹ It seems probable that adequate knowledge of the fundamental myocardial defects must be contingent upon a more thorough understanding of muscle physiology.⁶⁶

Attempts to produce heart failure under experimental conditions have met with some success. Using the heart-lung preparation, the administration of chloral hydrate, chloroform, potassium chloride or other agents which are noxious to the myocardium^{34, 45, 124} impairs the mechanical efficiency of the ventricles³⁴ causing dilatation of the heart, a rise in left and right intra-auricular pressures and a decrease in minute volume output of the ventricles. Similar results have been obtained in heart-lung preparations by the use of vasoconstricting drugs to reduce coronary flow^{123, 136} or by ligation of the coronary arteries.¹²⁴ In the study of circulatory dynamics use of the heart-lung preparation has offered certain fundamental suggestions of myocardial function;¹⁰¹ however, the usefulness of such

^{*} From the Cardio-Vascular Division, Department of Medicine, Washington University School of Medicine, St. Louis.

† Rockefeller Fellow in Cardiology 1948-49.

preparations is restricted and the qualitative nature of the myocardial injury producing heart failure is self-evident.

On the other hand, the use of the heart-lung^{105,124} and isolated heart preparations⁹⁴ have brought forward data on the energy metabolism of the normal and failing heart. Under normal conditions the heart performs increased mechanical work by virtue of its propensity to dilate optimally (i.e., by increasing initial fiber length). The performance of greater work and increased diastolic size is attended by an augmentation of oxygen consumption.^{32,124} Starling and Visscher¹²⁴ showed that the oxygen consumption of the heart varied with the initial length of its muscle fibers. Furthermore, convincing evidence has been evolved^{94,105} to show that as the heart becomes fatigued (and eventually fails), dilatation of the ventricles exceeds the limit normally required for optimum energy liberation. Oxygen consumption is further augmented. In spite of the greater dilatation and increased oxygen utilization the work output falls off and the mechanical efficiency of the heart becomes curtailed. These considerations are of great interest in the matter of clinical heart failure. The long-standing strains and resulting myocardial hypertrophy from chronic hypertension or valvular disease,^{39,51} and the restriction of coronary flow from these or other causes may seriously deplete the efficiency of the pump.

Experimental injury to the normal heart in animals with intact circulation is no less interesting. It has seemed rather striking that the infliction of injury to *localized* areas of the heart muscle may not induce heart failure so frequently. Coelho and Rocheta²⁰ and Orias¹⁰⁰ ligated the coronary arteries of the exposed hearts of dogs; they noted only occasionally the occurrence of failure and pulmonary edema. Likewise, it is often possible to produce large infarcts in such heart preparations without evidence of functional breakdown.⁴⁸ In a number of experiments Roos and Smith¹¹³ were able to ligate the three major coronary vessels

of the hearts of dogs so that only small segments of intact muscle were visible. Ventricular fibrillation frequently occurred but heart failure was not observed. The remarkable experience of Starr, Jeffers and Meade¹²⁷ is noteworthy. They burned the right ventricles of dogs with a cautery so that large masses of the muscle were rendered necrotic. Despite such severe damage heart failure was not noted; no conspicuous rise in venous pressure occurred except terminally in some instances. In contrast to these studies, experimental myocardial damage tending to involve *all or most* of the normal heart muscle has seemed more consistently to provoke cardiac decompensation. The administration of chloroform or potassium chloride⁵² or diphtheria toxin to dogs gives rise to some features of heart failure. However, cardiotoxins often exert deleterious effects on the peripheral vascular system so that the significance of dynamic changes may be difficult to judge in such experiments.

With the suggestion that generalized myocardial injury might significantly lower myocardial reserve and provoke failure, Roos and Smith¹¹³ exposed the hearts of dogs with intact circulation and inflicted heart muscle injury by embolization of the coronary vessels with starch granules. They were able to demonstrate widespread damage to the cardiac tissue. Furthermore, they found that acute congestive heart failure resulted rather consistently from this form of tissue insult, manifested by marked ventricular dilatation, a fall in arterial pressure and peripheral venous engorgement with hepatic and pulmonary congestion.

In the light of these experimental suggestions it is possible that heart failure may be associated with myocardial changes which functionally incapacitate all or most of the muscle even though morphologic muscle change may be slight or absent. Localized myocardial death, unless superimposed on established disease processes or unless productive of ventricular fibrillation, appears to be less apt to provoke myocardial decompensation.

DYNAMICS OF MYOCARDIAL FAILURE

The fluid dynamics of the normal heart and circulation, and the changes wrought by failure of the heart, are complex and

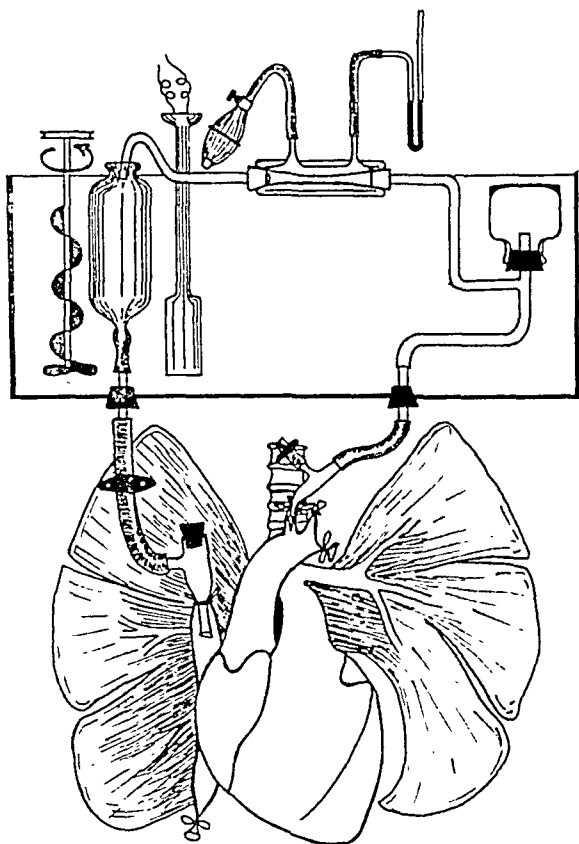


FIG. 1. Schematic diagram of the heart-lung preparation and heating unit as used in this laboratory. Venous reservoir and arterial connections of the preparation are enclosed in a constant temperature water bath. Note cannula tied into the superior vena cava which conducts blood from the venous reservoir to the right auricle. Arterial cannula is tied into the brachiocephalic artery which in the dog is the first branch of the aorta. The left subclavian artery and the aorta distal to it are securely ligated. The azygos vein and inferior vena cava are likewise tied off. Respiration is maintained by a Starling pump connected through an intratracheal cannula (not shown). A pinch clamp is usually applied to the venous tubing to regulate inflow and therefore output of the preparation. The peripheral resistance is secured by means of a section of Penrose tubing enclosed in a glass chamber; the tubing is compressed by air to any desired pressure. Such a preparation may be removed completely from the body of the dog but is usually left within the thoracic cage for mechanical stabilization.

difficult to describe. Although many facts are at hand pertaining to this problem, the interpretation of these factual data is by no means agreed upon. For the purposes of

this review, the more pertinent data will be presented briefly.

Starling's Experiments with the Heart-Lung Preparation: The Law of the Heart. In 1914 Patterson and Starling¹⁰¹ described the circulatory dynamics studied in the heart-lung preparation, amassing data from the wide experience of Starling and his pupils in the use of the preparation. (Fig. 1.) It should be recalled that the heart-lung preparation entails isolation of the cardio-pulmonary circulation from the body, using an artificial peripheral resistance. A venous reservoir is connected to the right atrium for the inflow of blood to the heart. The heart and lungs are entirely denervated. The arrangement permits the individual control of the venous inflow (and cardiac output), "arterial" resistance and heart rate within certain limits. The information derived from these studies has been considered fundamental and has had great bearing on studies of cardiovascular function to the present. The essential points of these studies may be described as follows:

Patterson and Starling pointed out that the heart muscle is analogous to skeletal muscle in that following a contraction the muscle fibers must be lengthened by some stretching force before another effective contraction can occur. The lengthening force to the ventricular muscle is provided by the inflow of blood from the atria. Normally the pressure of inflow to accomplish distention may be very small. If, then, the venous inflow is cut off, the ventricles do not dilate in diastole and the heart beats for a time in emptiness. Oppositely, if venous inflow is in operation and ventricular diastole should become greatly prolonged, the inflowing blood will forcibly distend the ventricles to the maximum extent. In the regularly beating preparation the occurrence of the succeeding ventricular contraction prevents extreme distention of the chamber. Therefore, in the properly functioning heart-lung preparation, with moderate peripheral resistance (i.e., 100 mm. Hg) and regular rhythm, the rate and pressure of venous inflow may be ad-

justed to fill the ventricles during diastole without causing undue distention. Cardiac output then equals venous inflow. If due care is taken to keep the blood fresh, this circulatory load may be compatible with long periods of function.

Now if the venous inflow is further increased, greater tension will be exerted on the ventricular walls by the inflowing blood during diastole, and the ventricles fill and distend more rapidly before the following systole halts the process. The result is an increase in stroke output and, with constant heart rate, an increased minute volume flow from the heart. It is clear from these experiments that in the heart-lung preparation the cardiac output can be augmented by increased return of blood to the heart. Patterson and Starling found that this increased inflow to the heart, however, was attended by an elevation of venous pressure. Changes occur in this picture if the heart begins to tire. Assuming the inflow is sustained, as the force of systolic ejection diminishes residual blood will remain in the ventricles at the end of systole tending to hold up blood entering from the atria. The venous pressure then will rise and a greater distending force against the ventricles occurs, becoming more pronounced as the power of systolic contraction is gradually lost. Under these conditions the elevated venous pressure is associated with decreased cardiac output. A picture then emerges which seems analogous to the venous hypertension of clinical heart failure.

Patterson and Starling further indicated that other means besides the elevation of venous pressure operate to increase cardiac output. By heating or cooling the preparation to change the heart rate, they were able to show that with a given constant venous inflow, alteration of heart rate does not change the cardiac output per minute. Changes in heart rate affect individual stroke volumes but the net output per minute remains the same. Under these conditions a more rapid heart rate lowers the venous pressure. It is obvious that adjustments in the preparation may be made

so that an increase in heart rate results in an *increase in cardiac output with the venous pressure remaining constant*. In order to do this a corresponding increase in venous inflow must be established.

The reports of Patterson and Starling are punctuated with the repeated observation that as a greater dilating force is applied to the ventricles they contract more vigorously. They point out a relationship between the diastolic volume and the energy output of the succeeding systole. This relationship was then described by Patterson, Piper and Starling¹⁰² as "the law of the heart." They state: "The law of the heart is therefore the same as that of skeletal muscle, namely, that the mechanical energy set free on passage from the resting to the contracted state depends on the area of 'chemically active surfaces'; i.e., on the length of the muscle fibers."

Patterson and Starling made the circum-spect statement that the dynamics of the heart-lung preparation are not strictly comparable to those in the intact animal and man. They were particularly concerned with the absence of negative intrapleural pressure effects in their experiments. In order to test negative pressure effect the hearts of heart-lung preparations were enclosed in cardiometers to which negative tension was applied. The results bore out the fact that readings in the venous manometers were reduced by the amount of the negative pressure used. Subsequently, Daly²⁴ enclosed heart-lung preparations in negative pressure chambers. He found that negative pressure expansion of the lungs produced a rise in cardiac output which he thought was due to the fall of resistance in the pulmonary vascular bed. Although the venous pressures were not reported in his paper, the trends indicate that ventricular filling was enhanced under negative pressure and that repercussions might be expected on the venous system in a lowering of venous pressure.

Measurement of Circulatory Flows and Pressures in Man. The perfection and utilization of the technic of right atrial catheterization

in man has broadened the horizons of study of cardiovascular physiology in normal persons and in those with heart disease. The essential features of the technic* need no introduction. In general, the method has proved of particular value in the

TABLE I
CARDIAC INDEX AND CARDIAC OUTPUT OF NORMAL HUMAN SUBJECTS

Author	Method Employed	Results
Cournand et al. ²³	Direct Fick	3.12 (2.12–4.01) (index)
Starr	Ethyl iodide	2.45 (index)
Nylin	Acetylene	2.46 (index)
Stead et al. ¹³²	Direct Fick	3.2 (2.6–3.9) (index)
Grollman ⁴⁷	Acetylene	2.2 (index)
McMichael et al. ⁸⁹	Direct Fick	5.3 L./min. (output)

recording of central venous, pulmonary arterial and right heart pressures. It has also provided a method of cardiac output determination when used in conjunction with the Fick principle³⁷ devised nearly eighty years ago. The Fick principle depends upon the calculation of the volume of blood passing through the lungs as determined by the uptake of oxygen and the rate of oxygen consumption. Details of the calculation will not be repeated here. The sampling of blood from the right atrial or ventricular cavity, made possible by the catheter method, provides a specimen of well mixed venous blood from all areas of the body. Although the cardiac output may be expressed in liter output per minute in individual cases, in order to unify the results relative to body size the output is frequently expressed as the minute volume output per square meter of body surface (i.e., cardiac index). Some workers^{28,89} have preferred to describe cardiac output in relation to oxygen consumption per minute.

Normal values for cardiac output and cardiac index in man are compiled from

* For history and technical details of the method cf. references in Richards' paper.¹¹²

the reports of several workers and are shown in Table I.

Although right heart catheterization and the Fick principle have been most widely utilized for cardiac output studies in recent years, it must be borne in mind that such

TABLE II
COMPARISON OF DIRECT FICK METHOD AND DYE METHOD IN ESTIMATING CARDIAC OUTPUT*

Patient	Direct Fick Method	Dye Method
Bronchiectasis, right pneumonectomy	4.7	5.5
Chronic emphysema, fibrosis	5.7	6.5
Normal	4.7	5.6
	10.1	13.6
Normal	7.1	9.6
	11.4	15.1
Normal	6.2	6.2
	8.2	8.4
Heart failure	4.1	3.1
Heart failure	5.7	5.6
Hypertension	6.2	5.0

* Compiled from the work of Hamilton et al.^{50a} showing cardiac output in liters per minute.

figures of cardiac output should be interpreted as indicating only general trends of output. Individual values should be evaluated with caution. Hamilton and a large group of co-workers^{50a} recently pointed out that the use of the dye method or the direct Fick procedure gave figures for cardiac output varying as much as 25 per cent in most instances. However, the results, with variable outputs, remained comparably similar. Therefore, employing either method, the trends of output become more reliable than do isolated values of output. There are errors and disadvantages in the use of either technic but it should be pointed out especially that the Fick principle, so widely used recently, is likewise vulnerable, for small differences in arteriovenous oxygen content may greatly magnify changes in the calculated cardiac output. (Table II.)

The effects on the dynamics of the heart and circulation of negative pressure, as shown by experiments on the heart-lung preparation, suggest that intrathoracic pres-

sure changes may exert important effects on cardiac performance in man. In this respect the contribution of Lauson and his associates⁷³ appears to be of importance. They studied the pressures in the right heart chambers, peripheral veins and systemic arteries in relation to various forms of respiration and in four instances with intrapleural pressure measurement. Their records show that during moderately deepened respiration a distinct pattern of pressure fluctuation is seen (both in the heart chambers and in the peripheral arteries) which are accentuated over the minimal fluctuations seen on quiet breathing. The tracings strikingly show that the fall of intra-auricular pressure associated with the onset of ventricular ejection is greater during inspiration than during expiration, due to the greater negativity of intrapleural pressure in the former. The difference in the pressure in the right atrium at the end of diastole and the pressure in the intrapleural space (the "net" auricular pressure) is increased in inhalation and lessens during exhalation. Similarly, the pressure in the right ventricle at the end of diastole and at the peak of the succeeding systole decreases during inspiration. At the height of inspiration these pressures, in relation to the negative intrapleural pressure (i.e., the "net" pressures), are increased just as in the case of the auricles. If the stroke volume of the right ventricle varies as a function of the *net* pressure of the filled ventricle at the end of diastole, an increase in stroke output of the right ventricle in inspiration occurs. Pressures in the femoral artery, recorded simultaneously, also indicate that left ventricular output waxes and wanes with expiration and inspiration, respectively. Lauson's group then brought forward evidence to show that these changes in right and left ventricular output, associated with respiration, are most probably due to changes in the resistance of the pulmonary vascular bed. In short, during inspiration more blood is held in abeyance in the lung and the left ventricular output decreases. In expiration, the opposite effects occur.

The lungs, therefore, function as a sponge absorbing and then releasing fluid with changes in capacity of its vessels.

The net pressure fluctuations measured by right heart catheterization delineate the essential features of Starling's law of the heart in the case of the right ventricle: the greater the net pressure at the end of diastole, the greater is the net pressure developed at the peak of the following contraction.

Lauson et al. were able to demonstrate that exaggerated breathing and the performance of the Valsalva or Mueller maneuvers produced striking changes in right auricular tension. Marked rise in intrapleural pressure was associated with elevation of pressure in the auricular chamber while forcefully induced negative pressure produced striking depressions of auricular tension.

The importance of such data is evident and must receive further consideration as other factors are brought out concerning heart failure.

Cardiac Output in Myocardial Insufficiency. From the rather didactic demonstrations in the isolated heart with controlled circulation¹⁰¹ one might expect that with a sustained venous return failure of the myocardium must be attended by a diminished systolic ventricular output. A reduction in cardiac output does, in fact, occur in many instances of heart failure reported in man.^{53, 55, 91, 111, 134} However, frequently in cardiac insufficiency in man, output of the heart may be within normal range or even elevated above normal standards. Summarizing his data of output determination, Harrison⁵³ noted that: (1) the cardiac output may be normal, decreased or increased in patients with congestive heart failure; (2) the average range and values for cardiac output are similar in patients with heart disease whether actual failure is in progress or not; (3) in congestive disease with clinical improvement there may be an increased, diminished or normal output; (4) apparently normal individuals may have output figures as low as those in patients with heart failure. The acetylene method of

outflow determination, with its inherent faults, was used in obtaining these data.* The technic of right heart catheterization and the Fick principle has, in general, confirmed Harrison's observations. Stead and his co-workers^{130,134} and Richards¹¹² have noted that in heart failure the cardiac output may be at normal standards, elevated or depressed. There is, nevertheless, a trend toward decreased cardiac output in cardiac insufficiency. Merrill⁹¹ found a normal range of cardiac index of 2.3 to 4.1 (average 3.3) in healthy persons. In twenty-three cases of congestive heart disease the average cardiac index was below the normal mean in twenty cases. In ten of these latter cases the cardiac index was below 2.3 which is the lowest limit of the normal standard.

However, Stead et al.¹³⁴ and others have expressed uncertainty as to the reason for the lack of correlation between the state of heart failure and the resting cardiac output. A number of workers have made empirical suggestions as to factors influencing cardiac output during failure.^{39,47,91} Stead, Warren and Brannon¹³⁴ studied two patients with severe anemia with congestive heart failure and two others in failure with thyrotoxicosis. These patients exhibited cardiac outputs that were considerably higher (cardiac indices of 4.5 or over) than is expected in persons of their size. These findings showed that congestive failure may develop in certain individuals before the resting cardiac output can fall to levels seen in normal subjects; this may be particularly true when thyrotoxicosis, anemia or other conditions are present to drive the cardiac output upward in response to the metabolic needs of the body. The suggestion is supported by the well known fact that anxiety¹³³ is one of the important causes of elevation of heart output in normal persons. Recently, augmented cardiac output has been noted in patients with thyrotoxicosis without circulatory insufficiency.¹³ Brannon and his group¹² determined the cardiac output in

eighteen patients with chronic anemia who did not have heart failure. In patients with hemoglobin values below 7 Gm. per cent and with hematocrits below 20 the cardiac output was usually elevated above resting output levels. In nine instances the hemoglobin was below 5 Gm. per cent and the average cardiac index was 6.5. Patients with moderate chronic anemia showed no significant changes in heart outflow. The results give added force to the suggestion that in a critical degree of anemia the blood requirements of the body are increased so that output and peripheral vascular flow¹ are elevated. If myocardial insufficiency develops, the cardiac output falls but it still may range within or above normal resting output.

In summary, the evidence indicates that heart failure occurs when the myocardium fails to deliver sufficient blood for body requirements, and the level of cardiac output may range from high to low (as against normal standards). The important consideration is that with cardiac failure the existing cardiac output, whatever its quantity, becomes *inadequate* to sustain normal body function.¹³⁰

Effects of Heart Failure on Venous Pressure; Influence of Changes in Blood Volume and in Arterial Resistance. It will be recalled that in the controlled circulatory preparation¹⁰¹ myocardial fatigue and failure of effective systolic ejection leads to increased residual ventricular blood at the end of systole. Inflow of blood to the heart is impeded and the venous pressure must rise. Dilatation of the heart occurs. Applied to the dynamics of the failing circulation in man this explanation for the elevation of venous tension seems simple and direct.^{53,99}

The reconstruction of events in congestive heart failure leading to venous hypertension may be put as follows:^{28,53} It is assumed that the right and left ventricles expel a given equal quantity of blood per stroke, but as a result of hypertension or other myocardial strain the stroke output of the left ventricle is reduced. Blood inflow to the left ventricle, however, remains unchanged; the left

* For methods of cardiac output previously employed refer to monographs of Grollman⁴⁷ and Harrison⁵³ and the paper of Hamilton.⁵⁰

ventricle now receives more blood than it ejects. The pulmonary venous and left auricular tensions must then rise. The venous pressure changes in these chambers is probably largely dissipated because of their distensibility. The left ventricle, in order to accommodate the inflowing blood as well as the residual blood after the previous beat, now dilates and the greater diastolic stretch of the muscle fibers provokes stronger systolic contraction. The stroke volume is augmented. The cardiac output may then be restored to its original value but at the expense of increased diastolic size and elevated venous tension. These events may occur repeatedly and in varying degree, finally to include the right ventricle, auricle and peripheral venous system.²⁸

Studies by Landis and his co-workers⁶⁸ indicate that changes in mechanics of circulation may lead to increase in venous pressure. They "exercised" normal, anesthetized dogs by electrical stimulation of the extremities. Such muscular activity evoked a tachycardia and a fall of venous pressure. When the myocardia of these dogs were damaged by interference with the coronary circulation, the venous tension did not rise during inactivity; however, when muscular movements were induced tachycardia occurred and venous pressure usually rose. In some experiments the venous pressure fell with muscular activity in dogs with damaged hearts but the fall was not so marked as in the animals with undamaged hearts. Unfortunately, these workers reported only very few experiments and none in which severe cardiac damage had been inflicted. Nevertheless, the evidence suggests that the picture of heart failure may be precipitated by physical activity when the "competence" of the heart muscle is impaired.

Observations on experimental heart failure were carried further by Roos and Smith.¹¹³ They produced extensive generalized cardiac damage, and failure of the heart occurred which was sudden in onset and characterized by cardiac dilatation,

elevation of intra-auricular tension and a decline in systemic arterial pressure. In experiments in which the blood volume was not increased by infusion, it was difficult to explain such abrupt changes in dynamics other than by the fundamental occurrence of cardiac dilatation and failure of effective systolic contraction. The dilatation then resulted in increased residual blood in the cardiac chambers in diastole, and entrance of blood from the venous system was then curtailed. It appeared to be failure of the heart to accept available blood from the veins that resulted in the increase of venous tension. Roos and Smith further showed that when the circulating blood volume was augmented by infusion, subsequent damage to the myocardium produced a more striking rise of venous pressure than was seen when the blood volume was not increased. In addition, quantitatively less myocardial injury was required to elevate the venous pressure and to produce cardiac dilatation and pulmonary congestion with the blood volume increased. It seems probable, therefore, that elevation of venous pressure is dependent further upon an abundant venous blood volume which is obstructed in its passage by incompetence of the heart muscle. The latter point finds further interesting support¹¹³ in that severe myocardial injury frequently provokes shock, so that the bulk of blood becomes immobile in the peripheral vascular bed. Both the venous pressure and the systemic arterial pressures are low. Under these conditions the picture of cardiac failure does not develop.

The manifestations of myocardial failure in the experiments described resemble those usually described under the term "backward failure" in clinical cases: There appears to be curtailed stroke output of the damaged heart and a failure of the organ to move blood from a vastly overfilled venous system. The interesting and well known corollary to these observations is found in severe myocardial failure with intense venous engorgement and pulmonary edema (especially when acute in onset) in which the rapid removal of blood from the "available"

venous supply, by phlebotomy or application of tourniquets to the extremities,^{27,58,63,74,141} may quickly permit recovery of the staggering heart muscle.^{11,61} The induction of drastic diuresis by mercurial or other preparations¹³⁵ may likewise cause marked improvement in severe heart failure with venous distention, possibly through a similar mechanism.

A number of investigators^{2,91,116,126,137} have been unable to accept as an adequate explanation the simple impounding of blood in the great veins for the rise in venous pressure in heart failure. Additional factors have been suggested. One consideration finding support in the opinions of several workers is the possibility of increased blood volume. Employing a dye technic, Gibson and Evans⁴⁴ noted in patients with heart disease that the blood volume increased as the severity of the heart failure increased. In these instances the hematocrit remained essentially unchanged, leading them to believe that cell volume and plasma volume increased proportionately. Meneely and Kaltreider⁹⁰ likewise evolved evidence suggesting a rise in blood volume in clinical heart failure. They were particularly struck by the high correlation between the degree of anoxemia and the increase in cell volume. The contention that hypervolemia occurs in patients with heart failure raises the important question of the possible effects on venous pressure and other manifestations of cardiovascular breakdown.

It may be re-stated here that the results of Roos and Smith¹¹³ indicate that deterioration in cardiac function may be intensified when the blood volume is augmented by infusion before cardiac damage is produced. It is possible, then, that in chronic heart disease extending over a longer period of time any increase in blood volume will hasten the development of myocardial decompensation. The observations of Murphy, Correll and Grill⁹⁷ give indubitable evidence that augmentation of the circulating volume in cardiac patients by venous infusion may produce a marked rise of venous pressure with danger of overwhelming the diseased

heart. In a group of interesting experiments Starr¹²⁶ found that the venous pressures of patients with congestive heart failure remained elevated after death. He could not account for the persistence of postmortem venous hypertension other than by excessive fluid content of the vascular system.

The mechanism of the increase in blood volume in congestive failure has been widely investigated. Particularly in recent years evidence has accumulated indicating that hypervolemia occurs with the retention of salt, and therefore of water, as a result of failure of renal elimination of salt. It has been shown in normal subjects that the administration of excessive amounts of salt will cause an increase in plasma volume, venous pressure and body weight.^{46,84} In terms of heart failure, this circumstance may be accentuated. Warren and Stead¹³⁷ studied two patients in congestive heart failure, in each of whom compensation was restored by the use of digitalis, a salt-free regimen and diuretics. Thereafter, salt was added to the diets and digitalis therapy was continued. In subsequent days the plasma volume increased and the gain in weight shown by these patients rather paralleled the augmentation of blood volume. However, the venous pressure did not become elevated with the increase in blood volume and these workers were not disposed to agree that hypervolemia necessarily provokes an increase in venous tension although it may become elevated in due time. Furthermore, they reasoned that the salt retention by the kidneys may be a function of decreased cardiac output rather than of venous engorgement of the kidneys. Merrill's conclusion took similar lines.⁹¹ He found a marked reduction in renal blood flow in cases of heart failure and noted that there was no significant correlation of venous pressure and renal flow in such cases. In addition, his evidence indicated that renal flow usually remained below 50 per cent of normal even though a reduction of venous pressure occurred. Merrill's study implied that sodium retention may result from a low glomerular fil-

tration rate secondary to decreased renal blood flow, for it was clearly demonstrated that inulin clearance (glomerular filtration) may be decreased from 33 to 50 per cent of normal in subjects with myocardial insufficiency. Assuming that tubular resorption is essentially normal in such subjects and that sodium filtration parallels that of inulin, reduced glomerular elimination of salt must occur. The consequent retention of sodium and of water then raises the blood volume, increasing cardiac load and enhancing the decline of the heart. Other studies^{43,119} have confirmed the fact that marked sodium retention occurs in congestive heart disease and may be the dominant factor in the precipitation of peripheral edema; the studies imply intravascular and extravascular increase of fluid volume. Experiments by Reichsman and Grant¹⁰⁸ yielded contrasting results. They studied patients with chronic rheumatic heart disease in congestive heart failure. Compensation of the heart was secured by digitalis therapy. When digitalis was subsequently discontinued, the hearts failed again, resulting in a rise in venous pressure. The subjects gained weight and peripheral edema later appeared. The same authors⁴⁶ studied the effect of excessive salt administration in normal subjects. They noted an increase in blood volume and weight but only with an increased venous tension. The experiments therefore suggest that "backward failure" occurred in the cardiac subjects.

The studies of blood volume in relation to heart disease have been held in some question, principally because of the errors known to occur in the use of the T-1824 dye technic of volume determination.¹⁰⁴ The loss of dye into the extracellular tissue spaces or into the lymphatic system, and the escape of the substance into various blood depots constitute serious objections to the procedure. Nevertheless, the method has yielded basically uniform results in the hands of various workers.^{28,44,90} Furthermore, Nylin and Hedlund^{99a} employed a method of blood volume determination

using erythrocytes tagged with radioactive phosphorus. They were able to reaffirm the occurrence of an increased blood volume in patients with failing hearts. The latter method confirmed the results of others employing the T-1824 method. Inherent faults in blood volume determinations are present but the tendency toward an increased blood volume in congestive failure seems amply established.

Although the blood volume has been considered of primary importance in heart failure, it has been suggested also that redistribution of blood within the vascular bed by vasoconstriction may influence the venous pressure.^{4,38} It has been noted clinically that the systemic blood pressure may be normal during periods of decreased cardiac output. However, that the blood pressure may reach high levels during heart failure is a matter of common knowledge to physicians. The pathogenesis of vasoconstriction in congestive failure is not clearly understood and, to date, the phenomenon has not been well reproduced under controlled, experimental conditions. Landis and his co-workers⁶⁸ maintained that vasoconstriction may be a compensatory reaction to venous engorgement. Other evidence⁹¹ has been advanced that vasoconstriction occurs in consequence of diminution of cardiac output. The direct importance of vasoconstriction in influencing the picture of heart failure is thus uncertain; however, it is possible that if the blood pressure is sufficiently elevated, not only is the direct load on the myocardium further increased but there may be inhibition of any trend toward shock. Pooling of peripheral blood is prevented and a greater quantity of blood may be impounded in the venous system.¹¹³

Hypothesis of Backward and Forward Failure.

Controversies concerning the mechanism of heart failure have chiefly centered about the train of events occurring in the wake of myocardial dilatation and diminution in cardiac output. An impressive body of evidence has been cited to support the view that curtailment of cardiac function may

diminish the acceptance of blood from the venous system by the heart. A rise of venous pressure then ensues if blood returns to the venous system from the peripheral bed at a greater rate than its passage into the heart ("backward failure"). As the blood volume later becomes increased, by decreased renal blood flow and possibly by a factor of renal engorgement, venous tension may be enhanced and peripheral edema occurs.^{16,84,108} This view has been challenged by those who consider that decreased cardiac output and consequent decreased renal blood flow, salt retention and increased blood volume are the first important events occurring in heart failure ("forward failure"). A rise of venous pressure, therefore, may not result from incompetence of heart action but follows when hypervolemia becomes established. These conflicts of views may be presented briefly. Stead and Warren¹³³ suggested that in patients with normal blood volume the level of venous pressure is not important in determining variations in cardiac output. In a wide variety of conditions a normal differential in pressure between the atrium and ventricle appeared to be adequate to maintain considerable increases in stroke volume.¹³⁸ On this basis, the suggestion was made that the Starling principle may not be applicable to cardiovascular dynamics in man in most instances. However, in subjects with low blood volume an increase in venous pressure was noted to accompany a rise of cardiac output. Furthermore, Stead and Warren¹³³ have stated that in patients with arteriovenous fistulas temporary interruption of the abnormal vascular communication results in an immediate drop in cardiac output. However, the right atrial pressure remains unchanged. They concluded that means other than venous pressure changes must be investigated to explain alteration in stroke volume in man.

The conclusions of Stead and Warren were criticized by Roos and Smith¹¹³ largely on the basis of errors that may arise on technical grounds. Since the work of Lauson et al.⁷³ indicated net right ventricu-

lar and auricular pressures are widely varied in respiration, the intra-auricular tension with respect to intrapleural pressure may not coincide with the actually recorded atrial pressure. Therefore it appears possible that the "effective" right auricular tension could have been elevated in the instances described. Furthermore, it may be pointed out¹¹³ that pitfalls may lie in the use of the intracardiac catheter, for a water manometer attached to the catheter tube may record auricular pressure only during inspiration. A corresponding rise of tension in expiration may not occur. A significant discrepancy between "effective" and apparent atrial tensions may thus arise from this technical factor. It is further apparent that the observation of an elevation of cardiac output without an increase in venous pressure does not invalidate the Starling principles. Recalling studies with the heart-lung preparation¹⁰¹ if the heart rate is increased, venous inflow and cardiac stroke output may be augmented without a rise of venous pressure. The indication is clear that in conditions in man in which heart rate is increased, an elevation of cardiac output may be achieved without a rise of venous pressure.

In this connection it is of interest that Cohen et al.²² found that cardiac output to be elevated in a number of patients with arteriovenous fistula. When the fistulas were closed temporarily, a decrease in cardiac output occurred together with a deceleration of heart rate. There was a concomitant fall in right atrial pressure. When the arteriovenous shunts were re-opened, the cardiac output and heart rate quickly rose; the right atrial tension likewise showed a small increase. The changes in auricular pressure were not of large magnitude, although the trend was consistent. These authors considered the variations in cardiac output in their subjects to be largely dependent on changes in heart rate rather than upon the altered levels of venous tension. Their findings are in general accord with the Starling principles in that altered rates of inflow to and output from the hearts were

accomplished with only small resultant changes in venous tension.

The experimental and clinical evidence at present is of insufficient scope to explain completely the mechanisms by which cardiac output is altered under normal and pathological conditions and the events contingent upon myocardial breakdown. The balance of evidence rather suggests that the phenomena of "backward failure" may be dominant in a given instance as heart failure begins, but the factors of "forward failure," including salt and fluid retention, become no less important as congestive failure progresses.

CONSEQUENCES OF HEART FAILURE

Pulmonary Edema. Of the vicissitudes to which the cardiac patient is subject, none is more dramatic than the occurrence of massive pulmonary edema. The condition has long been considered a manifestation of left ventricular failure.⁸³ Indeed this clinical impression was strengthened by early attempts to produce pulmonary edema experimentally. Many years ago Welch¹⁴² noted the occurrence of pulmonary edema resulting from ventricular overload following aortic constriction. Following this lead, other workers²¹ brought forth evidence to suggest that critical interference with function of the left ventricle may lead to massive edema of the lungs. The belief prevailed among these workers that edema of the lungs resulted directly from the intense congestion induced by myocardial failure. Furthermore, experiments in which the pulmonary veins or left auricle were constricted^{21,77,93,117} also induced pulmonary edema in some experiments. On the other hand Sahli¹¹⁷ and others^{55,77,93} were unable to confirm the contention that pulmonary edema resulted from drastic curtailment of left ventricular function. Other experimental evidence has been evolved to indicate that injury to the right ventricular muscle may likewise lead to acute and intense pulmonary edema.¹⁸ It is of further interest that acute pulmonary edema in patients with mitral stenosis is less common⁸³ although it is the

condition *par excellence* in which pulmonary venous drainage is expected to be impaired. The clinical and experimental evidence at hand, therefore, provides no certain clue as to the mechanism of acute pulmonary edema from failure of the myocardium. Pulmonary congestion alone does not appear to be the precipitating cause and other mechanisms must be investigated.

Diseases of the central and peripheral nervous systems may be complicated by pulmonary edema in the absence of demonstrable heart disease. Injuries of the head causing fracture of the skull, cerebral hemorrhage and tumor or infection of the brain^{83,140} may be complicated by a high incidence of lung edema. There is likewise ample experimental evidence to indicate that injury to nerves may produce pulmonary edema,^{35,36,121} such as stimulation of the stellate ganglia or of other structures of the vegetative nervous system.^{35,55,83,121} The frequent development of the condition following epinephrine administration in rabbits is well known.^{59,82} In the latter experiments the seizure can be controlled by central nervous system depressants such as morphine, papaverine and chloretone^{82,83} and aggravated by the stimulants metrazol and caffeine. These effects of the central nervous system on the vascular structure of the lungs are poorly understood. Many studies have shown that pulmonary circulation is under neurogenic control,^{25,26,54} and the possibility that "neurogenic" pulmonary edema is a result of excessive vasodilatation or diminished vasoconstriction has been strongly suggested by such studies. Furthermore, the possibility that nerve impulses may alter capillary permeability has been advanced and such a mechanism must be considered.³¹ Whether neurogenic edema is in any way related to the pulmonary edema of heart failure is uncertain at present.

The appearance of pulmonary edema following exposure to gaseous and parenteral toxins⁵⁵ has raised the possibility of a toxic mechanism in the pathogenesis of lung edema from heart disease. The frequent occurrence of spontaneous edema in the

heart-lung preparation appears to be due to a toxic agent, for it may result from the use of stored blood⁶⁷ or whipped blood.⁹⁸ In addition, the high protein content of the edema fluid indicates capillary damage, possibly toxic.⁹⁵ It has further been suggested that the lung edema frequently occurring in shock is due to the action of an "H-substance" carried to the lungs from the site of injury.⁹⁶

While there is doubt as to the primary agents in the production of pulmonary edema in man, the role played by secondary factors is more certain. The liability of the lung to edema because lymphatic drainage is "bottlenecked" by the anatomic limitations of the lymphatic system must be considered.³⁰ The ease of spread of fluid through the lung because of the absence of a true alveolar membrane and the many pores in the alveolar walls have been demonstrated.⁷⁶ The dependence of lung tissue upon alveolar air for oxygen makes it unusually susceptible to a rapidly spreading edema. As fluid accumulates in the lung it spreads easily and in so doing removes more lung tissue from its oxygen supply. The capillaries are rendered more permeable and accelerated filtration of fluid from the vessels into the airspace of the lung occurs.³⁰

Hepatic Congestion. Swelling and tenderness of the liver are frequent signs of a failing heart. The congestion of the central veins with hemorrhage, loss of central parenchymal cells, fibrosis and fat deposition are well known features of the "nutmeg" liver.⁷⁵ These changes have been ascribed to the high venous pressure of right heart failure.³⁹ On the other hand, the mechanical effect of venous congestion may not seem to offer a wholly adequate explanation for the central lesions. The direction of flow from the peripheral to the central hepatic veins indicates that the pressure in the peripheral veins must be the higher, yet the cells in the peripheral portion of the lobules are preserved. Furthermore, under the conditions of congestion the central veins are no more dilated than those about the lobular periphery. Other explanations for central he-

patic lesions have been advanced. Rich^{109,110} expressed the opinion that anoxemia resulting from venous stasis may produce such lesions. The location of the lesion and the occurrence of similar pathologic changes in anemia support the possibility.¹¹⁰ Mallory⁸⁶ proposed that central hepatic lesions result from toxemia or infectious processes. Nevertheless, it is possible to produce lesions closely resembling those of chronic passive congestion of the liver by obstructing the inferior vena cava and hepatic veins in experimental animals.^{8,147} Neither infection nor toxemia appear to be prerequisites. Although the lesion of central congestion, atrophy and fibrosis is almost wholly confined to cases of heart failure, other hepatic lesions have been noted. Katzin et al.⁶² reported 286 autopsied cases with chronic passive congestion of the liver. Of these forty-eight showed biliary or diffuse fibrosis of the liver.

The estimation of the frequency of true "cardiac cirrhosis" has been complicated by the multiplicity of definitions of the term. If "cardiac cirrhosis" is used to mean hepatic fibrosis in congestive failure, the condition is not rare; it may occur in 50 per cent of cardiacs who have been in failure for a period of nine months or more.⁶² If, however, the term refers to an atrophic, fibrosed liver with ascites and splenomegaly, the condition is uncommon.⁷⁵

Liver function is also disturbed in cardiac failure. Latent jaundice is frequently present, with serum bilirubin levels ranging from 0.5 mg. to 8 mg. per cent. Bromsulfalein excretion tests often show excessive retention with return to normal on compensation of the heart.^{5,7,75}

The pathogenesis of latent jaundice in heart failure is debatable. That there is an extrahepatic factor of excessive bilirubin formation seems quite certain. The elevation of stool and urine urobilinogen can be explained only on such a basis,¹⁰⁹ and the discovery of hemosiderin deposits in many organs is further evidence of extrahepatic jaundice.⁴⁰ The importance of the role of the liver is more uncertain. However, low

bilirubin tolerance⁷⁵ and the pathologic lesions in the liver suggest a definite hepatic influence although the severity of the lesions is often not in proportion to the degree of bilirubinemia.⁶²

Frank jaundice is uncommon in cardiac decompensation^{17,60,75} but its occurrence is considered an ill omen. That there is an additional factor to cause a transition from the latent jaundice of chronic passive congestion to frank clinical jaundice has been strongly suggested.⁷⁵ Pulmonary infarction frequently precedes the onset of jaundice. In one series studied by Kugel and Lichtman⁷⁵ 94 per cent of cardiac patients with clinical jaundice had pulmonary infarction. The hemolysis of red blood cells in the hemorrhagic lung infarct has been considered the source of the added bilirubin producing the jaundice.⁷⁵ Others have disagreed with this point of view.¹¹⁰ Whatever the mechanism of jaundice in these cases may be it is apparent that pulmonary infarction is the most frequent precipitating agent in cardiac jaundice.

Ascites occurs in 82 to 88 per cent of cardiac patients with heart failure, 15 per cent of whom require paracentesis.⁷⁵ The mechanism of its production is unknown; its occurrence suggests a true cirrhosis.⁷⁵ Other factors in the accumulation of ascites may be a low plasma protein and concentration of an antidiuretic substance. The urine of cirrhotic patients contains large amounts of an unmetabolized antidiuretic substance similar to the posterior pituitary principle.¹⁰⁶ The liver in heart failure may have a similar metabolic defect and the presence of such a substance may contribute to the formation of ascitic fluid and edema.

Edema. The pathogenesis of cardiac edema has been the object of much study and controversy. Many reviews of the subject have been written²⁸ and an extensive examination of the subject at this time would be repetitious.

The factors postulated by Starling²⁵ in the production of edema have been carefully analyzed and their importance in cardiac

edema investigated. The evidence indicates that of the theoretic factors productive of edema (increased capillary hydrostatic pressure, increased tissue osmotic pressure, decreased plasma osmotic pressure, decreased tissue tension or increased capillary permeability) only an increased capillary hydrostatic pressure seems to be of primary importance in the production of cardiac edema. Diminished plasma osmotic pressure due to hypoproteinemia does occur in many cardiacs^{56,103,115,120} but when present is of slight degree and is apparently not in itself sufficient to cause edema formation.² Increased capillary permeability due to anoxemia or dilatation⁶⁵ has been considered a possible factor^{3,70} and therapy with 45 per cent oxygen has been known to produce improvement and diuresis in patients.³ But the low protein content of cardiac edema fluid^{10,128,137} is strong evidence that there is no important capillary permeability increase, and an increase in permeability due to dilatation has been shown not to occur.⁷¹ Also, the frequent absence of edema in congenital cardiacs and in emphysematous patients who have severe anoxemia^{33,137} suggests that the degree of anoxemia seen in congestive heart failure does not in itself produce edema. In view of the low protein content of cardiac edema fluid an increase in tissue osmotic pressure can hardly be an important factor. In addition, there is no evidence that diminution in tissue tension is an important primary factor although in patients whose tissues have been previously distended by edema fluid the recurrence of edema may be facilitated. Lymphatic obstruction secondary to the rise in venous pressure has been considered a possible factor in formation of edema and has been found to be present,⁸⁸ yet the high protein content of lymphedema fluid²⁸ is quite unlike that of cardiac edema and doubt is cast on the importance of lymphatic obstruction in the pathogenesis of cardiac edema.

An excessive retention of salt and water by the kidney is known to occur in heart failure^{14,16,43,92,107} and has been considered

a primary factor in edema formation. The evidence indicates that there are two possible factors of dominant importance in the production of cardiac edema: an increase in capillary hydrostatic pressure and a retention of salt and water. Interpretation of the evidence concerning these disturbances has resulted in the postulation of two theories. According to the first, failure of the heart results in a rise in venous pressure which is reflected in a rise in capillary pressure⁷² which in turn causes increased filtration from the capillary extravascular fluid accumulation and reduction in circulating blood volume. Salt and water are retained by the kidney in an effort to restore blood volume.¹⁰⁴ Experimental and clinical evidence has shown that the rise in venous pressure is present in many cardiac patients,^{6,44,55,111} may be present in all under certain conditions and is reflected in a rise of capillary pressure.⁷² Such a pressure rise produced experimentally leads to the accumulation of edema fluid⁶⁴ similar in composition to that of cardiac edema fluid.^{69,103} The other theory emphasizes the salt and water retention, probably resulting from the diminution in cardiac output known to occur in many if not all patients in heart failure. Such retention increases blood volume and in so doing increases capillary hydrostatic pressure and filtration from the capillary. The rise in venous pressure is considered a secondary factor. The debate has not been reconciled.

Although many of the controversies in studies of the various phenomena of cardiac failure have been irreconcilable and confusing, the questions raised by such differences of opinion have stimulated further investigation of these problems. It is in re-study of controversial questions that the hope of greater knowledge lies.

SUMMARY

The mechanisms of cardiac failure are discussed as (1) injury of the myocardium leading to heart failure, (2) the dynamics of heart failure and (3) consequences of myocardial decompensation.

1. Myocardial injury may be judged frequently by morphologic changes in the hearts of persons who have died with heart failure. It is pointed out that the causes of functional breakdown of the heart are obscure but evidence suggests that generalized myocardial damage may be of prime importance in compromising cardiac function.

2. Studies by Starling and his pupils on the heart-lung preparation suggested certain principles of cardiodynamic function, some of which have been invoked to explain cardiodynamic changes in man. The more recent studies of cardiocirculatory problems in man, especially those utilizing the technic of right heart catheterization, are reviewed. The possible roles of cardiac output, increased blood volume and venous hypertension in the dynamics of heart failure are presented.

3. The pathologic physiology of pulmonary edema, hepatic congestion and peripheral edema in consequence of heart failure is briefly reviewed. The available evidence indicates that pulmonary edema may not result from simple congestion of lung tissue but that other factors, at present obscure, may operate in congested lungs to produce edema. Characteristic hepatic lesions and impairment of liver function may occur from congestive heart failure. The possible mechanisms of functional impairment, certain liver function tests and the occurrence of jaundice and ascites in heart failure are particularly discussed.

The authors are indebted to Dr. W. B. Wood, Jr., Department of Medicine, for many helpful criticisms in the preparation of this review.

REFERENCES

1. ABRAMS, D. I., FIERST, S. M. and FLACHS, N. Resting peripheral blood flow in the anemic state. *Am. Heart J.*, 25: 609, 1943.
2. ALTSCHULE, M. D. The pathological physiology of chronic cardiac decompensation. *Medicine*, 17: 75, 1938.
3. BARACH, A. L. and RICHARDS, D. W., JR. Effects of treatment with oxygen in cardiac failure. *Arch. Int. Med.*, 48: 325, 1931.
4. BAZETT, H. C. Blood volume and cardiovascular adjustments. *Am. Heart J.*, 21: 423, 1941.

5. BERNSTEIN, M., LE WINN, E. B. and SIMKINS, S. Heart disease and liver function. *J. Lab. & Clin. Med.*, 28: 1, 1942.
6. BLOOMFIELD, R. A. LAUSON, H. D., COUNRAND, A., BREED, E. S. and RICHARDS, D. W. Recording of right heart pressure in normal subjects and in patients with chronic pulmonary disease and various types of cardiovascular disease. *J. Clin. Investigation*, 25: 239, 1946.
7. BLUMBERG, N. and SCHLOSS, E. M. Effect of circulatory factors on bromsulfalein excretion in liver disease. *Am. J. M. Sc.*, 213: 470, 1947.
8. BOLTON, C. Pathological changes in the liver resulting from passive congestion experimentally produced. *J. Path. & Bact.*, 19: 258, 1914.
9. BOLTON, C. The pathology of cardiac dropsy. *Brit. M. J.*, 1: 642, 1917.
10. BRAMKAMP, R. G. Protein content of subcutaneous edema fluid in heart disease. *J. Clin. Investigation*, 14: 34, 1935.
11. BRAMS, W. A. and KATZ, L. N. Studies on the over-distended heart. I. Effects of venesection. *Am. J. Physiol.*, 98: 556, 1931.
12. BRANNON, E. S., MERRILL, A. J., WARREN, J. V. and STEAD, E. A. The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. *J. Clin. Investigation*, 24: 332, 1945.
13. BRANNON, E. S., STEAD, E. A. and WARREN, J. V. The cardiac output in thyroid disease. Quoted by Stead and Warren. *Arch. Int. Med.*, 80: 237, 1947.
14. BRIDGES, W. C. Low sodium diet and free fluid intake in the treatment of congestive heart failure. *New England J. Med.*, 234: 573, 1946.
15. BUDELMAN, G. and KARA-ENEFF, S. Ueber das Verhalten des Muskeltonus beim Aderlass. *Klin. Wchnschr.*, 19: 1103, 1940.
16. BURCH, G. E. Disturbances of water and salt balance in congestive heart failure. *Mod. Concepts Cardiovas. Dis.*, 17: 1948.
17. CANTAROW, A. Studies of hepatic function. *Arch. Int. Med.*, 56: 521, 1935.
18. CATALDI, G. M. Oedème aigu du poumon dans les lésions expérimentales du ventricule droit. *Arch. d. mal. du coeur*, 28: 604, 1935.
19. COELHO, E. and RIBIERO, M. Étude expérimentale sur deux formes pathogéniques de l'oedème aigu du poumon: mécanique et toxique. *Arch. d. mal. du coeur*, 29: 383, 1936.
20. COELHO, E. and ROCHETA, J. Recherches électrocardiographiques sur la ligature des artères coronaires chez le chien. *Compt. rend. Soc. de biol.*, 102: 203, 1929.
21. COELHO, E. and ROCHETA, J. Études expérimentales sur la pathogénie de l'oedème aigu du poumon. *Ann. méd.*, 34: 91, 1933.
22. COHEN, S. M., EDHOLM, E. G., HOWARTH, S., McMICHAEL, J. and SHARPEY-SCHAFER, E. P. Cardiac output and peripheral blood flow in arteriovenous fistula. *Clin. Sc.*, 7: 35, 1948.
23. COUNRAND, A., RILEY, R. L., BREED, E. S., BALDWIN, E. and RICHARDS, D. W. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. *J. Clin. Investigation*, 24: 106, 1945.
24. DALY, I. DEB. The resistance in the pulmonary vascular bed. *J. Physiol.*, 69: 238, 1930.
25. DALY, I. DEB. Physiology of the bronchial vascular system. *Harvey Lect.*, 31: 235, 1936.
26. DALY, I. DEB. Sensory receptors in the pulmonary vascular bed. *J. Exper. Physiol.*, 27: 123, 1937.
27. DANZER, C. S. The pathogenesis and treatment of dyspnea in the light of recent experiments. *Ann. Int. Med.*, 2: 239, 1928.
28. DAVIS, J. O. and SMITH, J. R. Pathogenesis of peripheral cardiac edema. *Am. J. Med.*, 3: 704, 1947.
29. DRINKER, C. K., PEABODY, F. W. and BLUMGART, H. L. Effect of pulmonary congestion on ventilation of the lungs. *J. Exper. Med.*, 33: 77, 1922.
30. DRINKER, C. K. Pulmonary Edema and Inflammation. Cambridge, 1945. Harvard Press.
31. ENGEL, D. Influence of the sympathetic nervous system on capillary permeability. *J. Physiol.*, 99: 161, 1940-41.
32. EVANS, C. L. and MATSUOKA, Y. The effect of various mechanical conditions on the gaseous metabolism and efficiency of the mammalian heart. *J. Physiol.*, 49: 378, 1915.
33. FAHR, G. and ERSCHLER, I. Studies of factors concerned in edema formation; hydrostatic pressure in capillaries during edema formation in right heart failure. *Ann. Int. Med.*, 15: 798, 1941.
34. FAHR, G. and BUEHLER, M. S. A physiologic definition of acute congestive heart muscle failure. *Am. Heart J.*, 25: 211, 1943.
35. FARBER, S. Pulmonary edema: vagotomy in the rabbit. *J. Exper. Med.*, 66: 297, 1937.
36. FARBER, S. Studies on pulmonary edema: the pathogenesis of neuropathic pulmonary edema. *J. Exper. Med.*, 66: 405, 1937.
37. FICK, A. Ueber die Messung des Blutquantums in den Herzventrikeln. *Sitzungsb. d. phys.-med. Gesellsch. zu Wurzburg*, 1870.
38. FINEBERG, M. H. and WIGGERS, C. J. Compensation and failure of the right ventricle. *Am. Heart J.*, 11: 255, 1936.
39. FISHBERG, A. M. Heart Failure. Philadelphia, 1940. Lea & Febiger.
40. FISHBERG, A. M. Jaundice in myocardial insufficiency. *J. A. M. A.*, 80: 1516, 1923.
41. FISHBERG, A. M., HITZIG, W. M. and KING, F. H. Circulatory dynamics of myocardial infarction. *Arch. Int. Med.*, 54: 997, 1934.
42. FRIEDMAN, B., CLARK, E. G., RESNIK, H. and HARRISON, T. R. Effect of digitalis on the cardiac output of persons with congestive heart failure. *Arch. Int. Med.*, 56: 710, 1935.
43. FUTCHER, P. and SCHROEDER, H. A. Studies on congestive heart failure. II. Impaired renal excretion of sodium chloride. *Am. J. M. Sc.*, 204: 52, 1942.
44. GIBSON, J. G. and EVANS, W. A., JR. Clinical studies of blood volume. III. Changes in blood volume, venous pressure and blood velocity rates in chronic congestive heart failure. *J. Clin. Investigation*, 16: 851, 1937.
45. GOLLWITZER-MEIER, KL. and KRUEGER, E. Herzenergetik und Strophanthinwirkung bei verschiedenen Formen der experimentellen Herzinsuffizienz. *Arch. f. d. ges. Physiol.*, 238: 251, 1936-37.

46. GRANT, H. and REICHSMAN, F. The effects of ingestion of large amounts of sodium chloride on the arterial and venous pressures of normal subjects. *Am. Heart J.*, 32: 704, 1946.
47. GROLLMAN, A. The Cardiac Output of Man in Health and Disease. Springfield, Ill., 1932. Charles C. Thomas.
48. GROSS, L., MENDLOWITZ, M. and SCHAUER, G. Hemodynamic studies in experimental coronary occlusion. i. Open chest experiments. *Am. Heart J.*, 13: 647, 1937.
49. GROSSMAN, M. Weitere experimentelle Beiträge zur Lehre von der Lungenschwellung und Lungenstarrheit. *Ztschr. f. klin. Med.*, 20: 397, 1892.
50. HAMILTON, W. F. Notes on the development of the physiology of cardiac output. *Federation Proc.*, 4: 183, 1944.
- 50a. HAMILTON, W. F., RILEY, R. L., ATTAYH, A. M., COUNNAND, A., FOWELL, D. M., HIMMELSTEIN, A., NOBLE, R. P., REMINGTON, J. W., RICHARDS, D. W., WHEELER, N. C. and WITHAM, A. C. Comparison of the Fick and dye methods of measuring cardiac output. *Am. J. Physiol.*, 153: 309, 1948.
51. HARRISON, T. R., ASHMAN, R. and LARSON, R. M. Congestive heart failure. *Arch. Int. Med.*, 49: 151, 1932.
52. HARRISON, T. R., FRIEDMAN, B. and RESNIK, H. Mechanism of acute experimental heart failure. *Arch. Int. Med.*, 57: 927, 1936.
53. HARRISON, T. R. Failure of the Circulation. Baltimore, 1939. Williams & Wilkins.
54. HEBB, C. O. Bronchomotor responses. *J. Physiol.*, 99: 67, 1940.
55. HENNEMAN, P. H. Acute pulmonary edema. *New England J. Med.*, 235: 590, 619, 1946.
56. HERMANN, G. R. Blood plasma proteins in patients with heart failure. *Ann. Int. Med.*, 24: 893, 1946.
57. HEYER, H. E. and HARRISON, T. R. Backward failure theory of congestive heart disease. *Mod. Concepts Cardiovas. Dis.*, 16, 1948.
58. HOWARTH, S., MCMICHAEL, J. and SHARPEY-SCHAFER, E. P. Effects of venesection in low output heart failure. *Clin. Sc.*, 6: 41, 1946.
59. JOHNSON, S. Experimental production and prevention of acute edema of the lungs in rabbits. *Proc. Soc. Exper. Biol. & Med.*, 25: 181, 1927-1928.
60. JOLLIFFE, N. Liver function in congestive heart failure. *J. Clin. Investigation*, 8: 419, 1929-1930.
61. KATZ, L. N. and BRAMS, W. A. Studies on the over-distended heart. ii. The rôle of relaxation in filling the distended and overdistended heart. *Am. J. Physiol.*, 98: 569, 1931.
62. KATZIN, H. M., WALLER, J. V. and BLUMGART, H. L. Cardiac cirrhosis of the liver. *Arch. Int. Med.*, 64: 457, 1939.
63. KOUNTZ, W. B., SMITH, J. R. and WRIGHT, S. T. Observations on the effect of tourniquets on acute cardiac crises, normal subjects, and chronic heart failure. *Am. Heart J.*, 23: 624, 1942.
64. KROGH, A., LANDIS, E. M. and TURNER, A. H. Movement of fluid through human capillary wall in relation to venous pressure and to colloid osmotic pressure of the blood. *J. Clin. Investigation*, 11: 61, 1932.
65. KROGH, A. Anatomy and Physiology of Capillaries. New Haven, 1922. Yale Univ. Press.
66. KUTSCHERA-AICHERGEN, H. Ueber Herzschwäche. *Wien. Arch. f. inn. Med.*, 18: 209, 1929.
67. LAMBERT, R. K. and GREMELS, H. On the factors concerned in the production of pulmonary edema. *J. Physiol.*, 61: 98, 1926.
68. LANDIS, E. M., BROWN, E., FAUTEAUX, M. and WISE, C. Central venous pressure in relation to cardiac "competence," blood volume, and exercise. *J. Clin. Investigation*, 25: 237, 1946.
69. LANDIS, E. M., JONAS, L., ANGEVINE, M. and ERB, W. Passage of fluid and protein through the human capillary wall during venous congestion. *J. Clin. Investigation*, 11: 713, 1932.
70. LANDIS, E. M. Micro-injection studies of capillary permeability. viii. Effect of oxygen lack on permeability of capillary wall to fluid and plasma proteins. *Am. J. Physiol.*, 83: 528, 1928.
71. LANDIS, E. M. Micro-injection studies of capillary permeability. *Am. J. Physiol.*, 81: 124, 1927.
72. LANDIS, E. M. Micro-injection studies of capillary blood pressure in human skin. *Heart*, 15: 209, 1929-1930.
73. LAUSON, H. D., BLOOMFIELD, R. A. and COUNNAND, A. The influence of the respiration on the circulation in man. *Am. J. Med.*, 1: 315, 1946.
74. LEMIERRE, A. and BERNARD, E. Recherches sur les indications et sur l'action physiologique de la saignée. *Presse méd.*, 34: 704, 1926.
75. LIGHTMAN, S. S. Diseases of the Liver, Gallbladder, and Bile Ducts. Philadelphia, 1942. Lea & Febiger.
76. LOOSLI, C. C. Interavascular communications in the lung. *Arch. Path.*, 24: 743, 1937.
77. LOWIT, M. Ueber die Entstehung des Lungenödem. Ein Beitrag zur Lehre von Lungenkreislauf. *Beitr. path. Anat. u. allg. Path.*, 14: 401, 1893.
78. LUBARSCII, O. Pathologische Morphologie und Physiologie des Ödems. *Zentralbl. f. Herz- u. Gefässkrankh.*, 4: 344, 1912.
79. LUISADA, A. A. and SARNOFF, S. J. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. *Am. Heart J.*, 31: 270, 1946.
80. LUISADA, A. A. and SARNOFF, S. J. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. ii. Mechanical and neurogenic elements. *Am. Heart J.*, 31: 282, 1946.
81. LUISADA, A. A. and SARNOFF, S. J. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. iii. Pharmacologic experiments. *Am. Heart J.*, 31: 293, 1946.
82. LUISADA, A. A. Beitrag zur Pathogenese und Therapie des Lungenödems und des Asthma Cardiale. *Arch. f. exper. Path. u. Pharmacol.*, 132: 313, 1928.
83. LUISADA, A. A. Pathogenesis of pulmonary edema. *Medicine*, 19: 475, 1940.
84. LYONS, R. H., JACOBSEN, S. D. and AVERY, N. L. Increase in the plasma volume following the administration of sodium salts. *Am. J. M. Sc.*, 208: 148, 1944.
85. MACK, I., GROSSMAN, M. and KATZ, L. N. The effect of pulmonary vascular congestion on the distensibility of the lungs. *Am. J. Physiol.*, 150: 654, 1947.

86. MALLORY, F. B. Chronic passive congestion of the liver. *J. M. Research*, 24: 455, 1911.
87. MCGUIRE, J., SHORE, R., HANENSTEIN, V. and GOLDMAN, F. Relation of cardiac output to congestive heart failure. *Arch. Int. Med.*, 63: 290, 1939.
88. McMASTER, P. D. Lymphatics and lymph flow in the edematous skin of human beings with cardiac and renal disease. *J. Exper. Med.*, 65: 373, 1937.
89. McMICHAEL, J. and SHARPEY-SCHAFER, E. P. Cardiac output in man by a direct Fick method. *Brit. Heart J.*, 6: 33, 1944.
90. MENEELY, G. R. and KALTREIDER, N. L. A study of the volume of blood in congestive heart failure. Relation to other measurements in fifteen patients. *J. Clin. Investigation*, 22: 521, 1943.
91. MERRILL, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of forward failure as the primary cause of edema. *J. Clin. Investigation*, 25: 389, 1946.
92. MERRILL, A. J. Mechanism of salt excretion in congestive heart failure. *Proc. Am. Federation Clin. Research*, 2: 8, 1946.
93. MODRAKOWSKI, G. Beobachtungen an der überlebenden Säugetierlunge. II Mitteilung. Über die experimentelle Erzeugung von Lungenödem. *Arch. ges. Physiol.*, 158: 527, 1914.
94. MOE, G. K. and VISSCHER, M. B. The mechanism of failure in the completely isolated mammalian heart. *Am. J. Physiol.*, 125: 461, 1939.
95. MOON, V. H. Experimental pulmonary edema. *Arch. Path.*, 21: 565, 1936.
96. MOON, V. H. Shock mechanisms and pathology. *Arch. Path.*, 24: 642, 794, 1937.
97. MURPHY, F. D., CORRELL, H. and GRILL, J. C. The effects of intravenous solutions on patients with and without cardiovascular defects. *J. A. M. A.*, 116: 104, 1941.
98. NEWTON, W. H. Pulmonary edema in the cat heart-lung preparation. *J. Physiol.*, 75: 288, 1932.
99. NYLIN, G. On the amount of, and changes in, the residual blood of the heart. *Am. Heart J.*, 25: 598, 1943.
- 99a. NYLIN, G. and HEDLUND, S. Weight of the red blood corpuscles in heart failure determined with labelled erythrocytes during and after decompensation. *Am. Heart J.*, 33: 770, 1947.
100. ORIAS, O. The dynamic changes in the ventricles following ligation of the ramus descendens anterior. *Am. J. Physiol.*, 100: 629, 1932.
101. PATTERSON, S. W. and STARLING, E. H. On the mechanical factors which determine the output of the ventricles. *J. Physiol.*, 48: 357, 1914.
102. PATTERSON, S. W., PIPER, H. and STARLING, E. H. The regulation of the heart beat. *J. Physiol.*, 48: 465, 1914.
103. PAYNE, S. A. and PETERS, J. P. Plasma proteins in relation to blood hydration. VIII. Serum proteins in heart disease. *J. Clin. Investigation*, 11: 103, 1932.
104. PETERS, J. P. Role of sodium in the production of edema. *New England J. Med.*, 239: 353, 1948.
105. PETERS, H. C. and VISSCHER, M. B. The energy metabolism of the heart in failure and the influence of drugs upon it. *Am. Heart J.*, 11: 273, 1936.
106. RALLI, E. P., RABSON, J. S., CLARKE, D. and HOAGLAND, C. L. Factors influencing ascites in patients with cirrhosis of the liver. *J. Clin. Investigation*, 24: 316, 1945.
107. REASER, P. B. and BURCH, G. E. Radiosodium studies in congestive heart failure. *Proc. Soc. Exper. Biol. & Med.*, 63: 543, 1946.
108. REISCHMAN, F. and GRANT, H. Some observations on the pathogenesis of edema in cardiac failure. *Am. Heart J.* 32: 438, 1946.
109. RICH, A. R. Pathogenesis of forms of jaundice. *Bull. Johns Hopkins Hosp.*, 47: 338, 1930.
110. RICH, A. R. and RESNICK, W. H. On the mechanism of jaundice following pulmonary infarction in patients with heart failure. *Bull. Johns Hopkins Hosp.*, 38: 75, 1926.
111. RICHARDS, D. W. JR., COURNAND, A., DARLING, R. C., GILLESPIE, W. H. and BALDWIN, E. Pressure of the blood in the right auricle, in animals and man: under normal conditions and in right heart failure. *Am. J. Physiol.*, 136: 115, 1942.
112. RICHARDS, D. W., JR. Contributions of right heart catheterization in the physiology of congestive heart failure. *Am. J. Med.*, 3: 434, 1947.
113. ROOS, A. and SMITH, J. R. The production of experimental heart failure in dogs with intact circulation. *Am. J. Physiol.*, 153: 558, 1948.
114. RÖSSLER, R. Ueber experimentelle Herzschädigung durch Koronargefäßverengung und ihre Beeinflussung durch Pharmaka. *Arch. f. exper. Path. u. Pharmacol.*, 153: 1, 1930.
115. ROWE, A. H. Refractometric studies of serum proteins in nephritis, cardiac decompensation, diabetes, anemia and other chronic diseases. *Arch. Int. Med.*, 19: 354, 1917.
116. RYDER, H. W., MOLLE, W. E. and FERRIS, E. B. The influence of the collapsibility of veins on venous pressure, including a new procedure for measuring tissue tension. *J. Clin. Investigation*, 23: 333, 1944.
117. SAHLI, H. Zur Pathologie und Therapie des Lungenödems. *Arch. f. exper. Path. u. Pharmacol.*, 19: 433, 1885.
118. SCHLOMKA, G. Commotio cordis and ihre Folgen. Die Einwirkung stumpfer Brustwandtraumen auf des Herz. *Ergebn. inn. Med. u. Kinderheilk.*, 47: 1, 1934.
119. SCHROEDER, H. A. Studies on congestive heart failure. I. The importance of restriction of salt as compared to water. *Am. Heart J.*, 22: 153, 1941.
120. SEYMOUR, W. B., PRITCHARD, W. H., LANGLEY, L. P. and HAYMAN, J. M. Cardiac output, blood and interstitial fluid volume, total circulating serum protein and kidney function during cardiac failure and after improvement. *J. Clin. Investigation*, 21: 229, 1942.
121. SHORT, R. H. D. Pulmonary changes in rabbits after bilateral vagotomy. *J. Path. & Bact.*, 56: 355, 1944.
122. SMITH, J. R. and JENSEN, J. Observations on the effect of theophylline aminoisobutanol in experimental heart failure. *J. Lab. & Clin. Med.*, 31: 850, 1946.
123. SOCIN, C. Experimentelle Untersuchungen über

- akute Herzschwäche. *Arch. ges. Physiol.*, 160: 132, 1914-1915.
124. STARLING, E. H. and VISSCHER, M. B. The regulation of the energy output of the heart. *J. Physiol.*, 62: 243, 1927.
 125. STARLING, E. H. Physiological factors involved in causation of dropsy. *Lancet*, 1: 1267, 1896.
 126. STARR, I. Role of the "static blood pressure" in abnormal increments of venous pressure. II. Clinical and experimental studies. *Am. J. M. Sc.*, 199: 40, 1940.
 127. STARR, I., JEFFERS, W. A. and MEADE, R. H. The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease. *Am. Heart J.*, 26: 291, 1943.
 128. STEAD, E. A. and WARREN, J. V. Protein content of extracellular fluid in normal subjects after venous congestion and in patients with cardiac failure, anoxemia and fever. *J. Clin. Investigation*, 23: 283, 1944.
 129. STEAD, E. A., WARREN, J. V. and BRANNON, E. S. Cardiac output in congestive heart failure. *Am. Heart J.*, 35: 529, 1948.
 130. STEAD, E. A. Relation of cardiac output to symptoms and signs of congestive heart failure. *Mod. Concepts Cardiovas. Dis.*, 16: 1948.
 131. STEAD, E. A. and EBERT, R. V. Shock syndrome produced by failure of the heart. *Arch. Int. Med.*, 69: 369, 1942.
 132. STEAD, E. A., WARREN, J. V., MERRILL, A. J. and BRANNON, E. S. The cardiac output in male subjects as measured by the technique of right atrial catheterization. *J. Clin. Investigation*, 24: 326, 1945.
 133. STEAD, E. A. and WARREN, J. V. Cardiac output in man. *Arch. Int. Med.*, 80: 237, 1947.
 134. STEAD, E. A., WARREN, J. V. and BRANNON, E. S. Cardiac output in congestive heart failure. An analysis of the reasons for the lack of correlation between the symptoms of heart failure and the resting cardiac output. *Am. Heart J.*, 35: 529, 1948.
 135. STEINBERG, F. U. and JENSEN, J. The effect of theophylline aminoisobutanol on the circulation in congestive heart failure. *J. Lab. & Clin. Med.*, 31: 857, 1946.
 136. VISSCHER, M. B. The restriction of the coronary flow as a general factor in heart failure. *J. A. M. A.*, 113: 987, 1939.
 137. WARREN, J. V. and STEAD, E. A., JR. Fluid dynamics in chronic congestive heart failure. *Arch. Int. Med.*, 73: 138, 1944.
 138. WARREN, J. V., BRANNON, E. S., STEAD, E. A., JR. and MERRILL, A. J. The effect of venesection and the pooling of blood in the extremities on the arterial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances. *J. Clin. Investigation*, 24: 337, 1945.
 139. WARREN, J. V., STEAD, E. A., JR. and BRANNON, E. S. The cardiac output in man. A study of some of the errors in the method of right heart catheterization. *Am. J. Physiol.*, 145: 458, 1946.
 140. WEISMAN, S. S. Edema and congestion of the lungs from intracranial hemorrhage. *Surgery*, 6: 722, 1939.
 141. WEISS, S. and ROBB, G. P. Treatment of cardiac asthma (paroxysmal cardiac dyspnea). *M. Clin. North America*, 16: 961, 1933.
 142. WEICHL, W. H. Zur Pathologie des Lungenödems. *Virchows Arch. f. path. Anat.*, 72: 375, 1878.
 143. WHITE, H. L. Measurement of cardiac output by a continuously recording conductivity method. *Am. J. Physiol.*, 151: 45, 1947.
 144. WINSOR, T. and BURCH, G. E. Use of the phlebomanometer: normal venous pressure values and a study of certain clinical aspects of venous hypertension in man. *Am. Heart J.*, 31: 387, 1946.
 145. WITT, D. B., LINDNER, E. and KATZ, L. N. The dynamic effect of acute experimental poisoning of the heart with diphtheria toxin. *Am. Heart J.*, 13: 693, 1937.
 146. YEOMANS, A., PORTER, R. R. and SWANK, L. Observations on certain manifestations of circulatory congestion produced in dogs by rapid infusion. *J. Clin. Investigation*, 22: 33, 1943.
 147. ZIMMERMAN, A. M. and HILLSMAN, J. A. Chronic passive congestive of the liver. *Arch. Path.*, 9: 1154, 1930.

Combined Staff Clinics

Cholesterol Metabolism and Arteriosclerosis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. DAVID SEEGAL: This clinic is concerned with an examination of the possible role of a disordered cholesterol metabolism in the pathogenesis of atherosclerosis and arteriosclerosis. This problem has engaged many investigators and has led to considerable controversy. We shall limit ourselves to a small segment of the field. For more general and complete discussions you might consult the reviews of Cowdry,¹ Duff,² Winternitz,³ Hueper⁴ and a recent Biological Symposium.⁵ These reports contain excellent presentations of current hypotheses concerning the causation of atherosclerosis, including mechanical factors, cholesterol, arterial vascularization and colloid imbalance.

Atherosclerosis is characterized by the deposition of lipid substances in the intima. We consider atherosclerosis to be an early manifestation of arteriosclerosis. Both the early and late stages of arteriosclerosis may be present without symptoms. With progressive vascular damage, signs of illness usually appear because of an inadequate flow of blood through the coronary, cerebral or peripheral arteries.

The medical and socio-economic importance of arteriosclerosis requires no em-

phasis in this clinic. It is disappointing, however, that so little is known about its cause, natural history, treatment or prevention. Yet arteriosclerosis is probably responsible for more disability and death than any other single cause of disease.

Among the reasons for this slow development in our knowledge is that present methods for the diagnosis of arteriosclerosis are not much improved over those available thirty years ago. We still make the diagnosis of arteriosclerosis on the basis of such presumptive evidence as old age, or *post hoc* when organic impairment has been produced by occlusive arterial disease. Even after an individual is subjected to complete study we have great difficulty determining the presence, distribution and severity of arteriosclerosis. We are often confused in trying to discriminate between the relative preponderance of intimal and medial sclerosis, which are quite different pathologic entities. These limitations are increased by what Dr. Wolbach described as the "vagaries" of arteriosclerosis—the disparity in the extent of the process in some vessels as compared with others in the same individual. Furthermore, it is not unusual to observe early and advanced lesions of arteriosclerosis side by side in the same aorta. The differences in age of contiguous plaques would suggest that the causative agent acts discontinuously.

Our fallibility in the diagnosis of arteriosclerosis is more clearly shown when we carry out the orderly sequences of history and physical examination. The reports of Musser, White and Boas have called attention to the importance of information

¹COWDRY, E. V. Arteriosclerosis: A Survey of the Problem. New York, 1933. McMillan.

²DUFF, L. Experimental cholesterol arteriosclerosis and its relationship to human arteriosclerosis. *Arch. Path.*, 20: 81-123, 257-304, 1935.

³WINTERNITZ, M. C. The Biology of Arteriosclerosis. Springfield, Ill., 1938. C. C. Thomas.

⁴HUEPER, W. C. Arteriosclerosis: a general review. *Arch. Path.*, 38: 162-181, 245-285, 350-364, 1944; 39: 51-65, 117-131, 187-216, 1945.

⁵Biological Symposia. Vol. xi. Aging and Degenerative Diseases. Lancaster, Pa., 1945. J. Cattell Press.

concerning the family history in special instances of arteriosclerosis. More detailed data are required in this category. In the past and present history a well documented episode of myocardial infarction is good evidence for the presence of arteriosclerosis. Similarly, clinical patterns associated with occlusion of the arteries to the brain or lower extremities yield useful information in the diagnosis of arteriosclerosis.

The physical examination may be helpful or misleading. The wide pulse pressures in elderly individuals without overt aortic insufficiency reflect the relative inelasticity of the long tubes beyond the aortic arch. Retinal study may show arteriosclerotic changes but this finding does not necessarily indicate the presence or degree of this disease in other vessels. Severe arteriosclerosis of the coronary arteries is found frequently in individuals whose eyeground examination is reported normal. Too often thickened or even beaded radial arteries lead to the diagnosis of general arteriosclerosis. In the great majority of these cases the abnormality in the radial artery is the result of medial (Mönckeberg) and not intimal sclerosis. When a diagnosis is obscure, the general appearance and the age of a patient often leads to the presumptive diagnosis of "general arteriosclerosis" as the chief cause of a patient's disability. Dr. K. B. Turner and I found "general arteriosclerosis" one of the most frequent erroneous diagnoses in the medical clinicopathology records of this hospital between 1917 and 1935.

Certain x-ray methods are rewarding in the diagnosis of arteriosclerosis. Isolated calcified plaques are sometimes visualized in various portions of the aorta. Calcified rings may be demonstrated in the aortic valve area by the technic of Sosman. Medial arterial calcification is seen in x-rays of the extremities and intimal sclerosis may be detected by using contrast media. Calcified areas in the renal, mesenteric and cerebral arteries may be seen from time to time. However, x-rays are of little service in the detection of coronary arteriosclerosis.

There are no chemical tests for arteriosclerosis.

We are forced to conclude that we lack methods to diagnose and quantitate the degree of arteriosclerosis in man.

Nor do the data now available, whether experimental or clinical, afford a sound basis for the treatment of arteriosclerosis. Work indicating that diets low in certain foodstuffs might diminish or reverse arteriosclerosis is suggestive but too new to be evaluated.

Before considering the evidence bearing on the relation of cholesterol to arteriosclerosis, I have asked Dr. Bevans to describe the pathologic sequences in arteriosclerosis. She will show that arteriosclerosis is not an inevitable concomitant of aging. She will further comment on the vagaries of arteriosclerosis and on the disparity in age of contiguous lesions in the aorta.

DR. MARGARET BEVANS: Before describing the development of arteriosclerotic lesions in man I should like to call attention to two anatomic changes which normally occur in the arteries: First, the intima of the aorta increases from a single layer of endothelial cells in the newborn to a well defined fibrous layer lined by endothelium in the adult. Secondly, the elastic tissue in the wall of all arteries deteriorates progressively throughout the life span. The consequent stretching is apparent to all of us who have followed the evolution of our own temporal arteries. This is *not* arteriosclerosis.

For purposes of this discussion, we shall consider atherosclerosis as an early stage of arteriosclerosis, being fully aware that this is a controversial point. The earliest lesion which pathologists can recognize is the deposition of lipid material beneath the endothelium of the intima. Even at this early stage the lipid is found there in star-shaped connective tissue cells, extracellularly in the tissue spaces and in macrophages which have a foamy cytoplasm. Dissolution of some of the macrophages occurs and cholesterol and fatty acid crystals are found in the layers of the intima. The adjacent fibrous tissue undergoes a

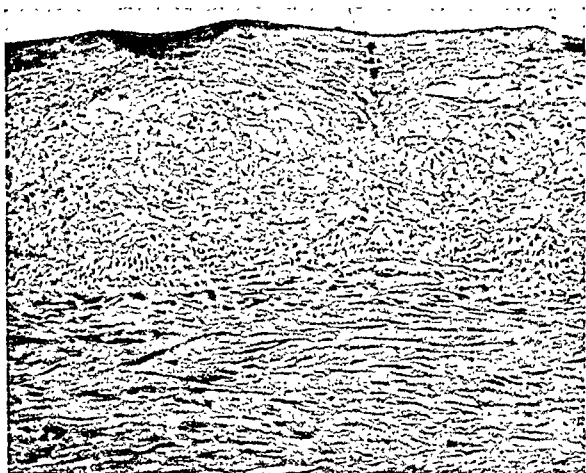


FIG. 1. Human arteriosclerosis; section of aorta showing moderately advanced intimal arteriosclerosis. A fibrous tissue layer covers the foamy cells giving a white appearance to the plaque in the gross specimen; hematoxylin and eosin stain, $\times 163$.

degenerative change characterized by breaking up of the fibrillar strands into a granular substance. Proliferation of the superficial intimal fibrous tissue results in thickening of the intima above the deposit. (Fig. 1.) This process is reflected by the yellow streaks and the white and yellow raised plaques on the intimal surface, the white areas being those with the thicker layer of overlying fibrous tissue. Up to this point the alteration can be considered atherosclerosis. Changes subsequent to the formation of the atheromatous plaques are various and unpredictable. They are all grouped under the heading of arteriosclerotic lesions but before I describe them I should like to emphasize three facts: (1) There is a gradual merging of these changes with the atheromatous stage described previously. (2) Almost invariably all of these changes can be found in the same artery. (3) To the best of my knowledge no relation of lesions to intervals of time has been established.

The deeper layers of the atheromatous plaques undergo necrosis and calcium is deposited in these areas. (Fig. 2.) Eventually the entire plaque and the overlying intima may be converted into a mass of calcium. More often the increased rigidity due to calcium within the plaque causes stretching and injury to the superficial



FIG. 2. Human arteriosclerosis, advanced lesion; the intimal plaque is composed of a dense layer of fibrous tissue; thrombus is seen on the surface. Deep in the plaque calcium has been deposited and the media is compressed beneath the plaque; hematoxylin and eosin stain, $\times 20$.

intima layers sufficient to produce ulceration. Necrosis of the deeper layers of the atheromatous plaque may spread upward before calcification occurs. When this happens the superficial layers of the intima ulcerate and a mass of soft atheromatous material is swept into the blood stream leaving a rough base in which many anisotropic cholesterol crystals may be identified. With the interruption of the endothelial lining of the intima the familiar sequelae of thrombus formation and organization ensue. Intramural hemorrhages about the atheromatous and sclerotic plaques must also be mentioned. These cause further damage to the vascular wall.

Since this type of arteriosclerosis is essentially a disease of the intima, we shall not discuss changes in the media except to say that they occur secondary to changes in the intima.

We have no explanation to offer for the vagaries of distribution of arteriosclerosis. Some workers have believed that strain on the thinner areas where branching occurs plays a part in the localization of sclerotic plaques but this is not invariably the observed distribution. Others have suggested that increased blood pressure plays an important part in the development of the plaques, citing as examples the occurrence

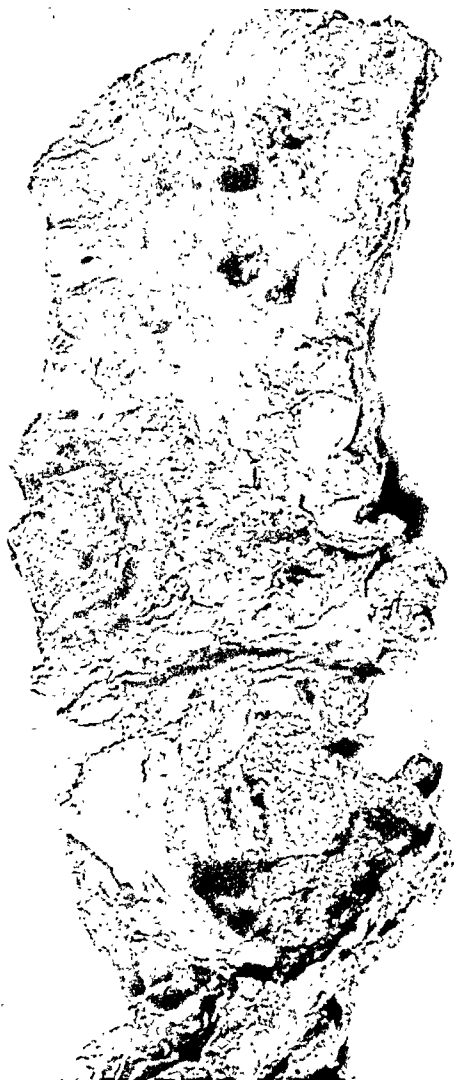


FIG. 3. Human aorta with severe arteriosclerosis illustrating the progressive nature of the disease. Small yellow plaques representing the earliest lesions lie close to old ulcerated plaques.

of pulmonary artery sclerosis principally in the presence of pulmonary hypertension and the severe generalized arteriosclerosis that is often the companion of systemic hypertension.

It has long been recognized by pathologists that arteriosclerosis bears no absolute relation to age though its incidence certainly increases with the years. We are accustomed to seeing aortas and coronary arteries almost entirely free of sclerosis in elderly people. We also find advanced sclerosis in individuals before the fourth decade of life. The recent review of the Army Medical Museum material by Yater

indicates the frequency of diffuse coronary artery disease in persons below the age of forty, the necropsy material comprising over 400 men with diffuse coronary sclerosis. In this series individuals with a familial history of hypertension were four times as frequent as those without such a background.

Is arteriosclerosis a continuously progressive disease? Side by side in most sclerotic vessels there are early atheromatous plaques and old calcified ulcerated lesions. (Fig. 3.) This suggests that arteriosclerosis is a reaction to discontinuous stimuli which may occur at any time in the life of an individual.

In summary, the earliest detectable lesions of human arteriosclerosis are deposits of lipoid in the intima. Necrosis, calcification and ulceration of atheromatous material in the initial deposit follow in undetermined periods of time. The reasons for the localization of plaques are not altogether clear. Arteriosclerosis bears no absolute relation to age and seems to be a discontinuous disease process.

DR. SEEGAL: We shall now consider the evidence relating arteriosclerosis to cholesterol metabolism. There are three chief reasons for the interest of investigators in such a relation. In the first place, cholesterol and its esters occur in considerable amounts in arteriosclerotic plaques. Secondly, it has been possible to produce arteriosclerosis by feeding excess cholesterol to rabbits, guinea pigs and chickens; moreover, Dr. Steiner and Dr. Kendall have found that lesions closely resembling those seen in human arteriosclerosis develop in the dog following the ingestion of cholesterol and thiouracil over a prolonged period. Finally, it is a common clinical experience that arteriosclerosis develops prematurely and with great severity in such diseases as uncontrolled diabetes mellitus and chronic glomerulonephritis. Hypercholesterolemia is common in these conditions.

Dr. Batchelor will review some of the pertinent facts regarding cholesterol metabolism.

DR. WILLIAM H. BATCHELOR: Cholesterol, like the bile acids, sex hormones, hormones

of the adrenal cortex and pro-vitamin D, is a sterol, one of a group of polycyclic compounds found in all plant and animal tissues, "neutral and comparatively stable substances which occur partly in the free condition and partly esterified with higher fatty acids."⁶ Cholesterol is quantitatively the most important sterol of animal tissues. "It is present in all cells of the animal organism, in largest amounts in the brain and nerve tissue, in the suprarenal glands, and in egg yolk. The solid matter of the human brain contains as much as 17% of the substance."⁶

Relevant to our discussion today is the finding of Schoenheimer and others that cholesterol constitutes 40 to 65 per cent of the phospholipid-free fats extracted from arteriosclerotic lesions of human aortas. Moreover, and this may prove to be of special interest as regards arteriosclerosis, Ruzicka and his co-workers were able to identify at least four oxidation products of cholesterol in the lipids obtained from arteriosclerotic human aortas, namely, $\Delta^{3,5}$ cholestadiene-7-one, $\Delta^{4,6}$ cholestadiene-3-one, 7- β hydroxycholesterol and 3,5,6 cholestantriol. (Fig. 4.) The presence of these compounds suggests the possibility of oxidative metabolism of cholesterol in the body. The physiologic significance of some of these substances is now under investigation by Dr. Kendall and his co-workers.

In addition to these oxidation products of cholesterol, a reduction product, the saturated compound dihydrocholesterol, has been found in small amounts in the sterols isolated from various organs (Schoenheimer).

The cholesterol of the diet can be absorbed in the small intestines. In cholesterol feeding experiments the ease with which it is absorbed depends upon its physical state. In finely divided form or in solution in fats, it is readily absorbed; fed in crystalline form it is largely excreted unchanged.

In man about 0.5 Gm. of cholesterol is secreted into the intestines each day in the

bile. This is probably largely reabsorbed. The major part of the sterols excreted in the feces are the reduction products of cholesterol designated coprosterol and dihydrocholesterol. These reduced sterols are not reabsorbed to any important degree. The mechanism of their reduction is not clear. It has been suggested that it is the result of the action of bacterial flora of the large intestines. Since reduction of cholesterol *in vitro* does not yield coprosterol, a direct reduction of cholesterol seems unlikely. Experiments on both dog and man indicate that cholestenone is an intermediate in the biochemical conversion of cholesterol to coprosterol.

Cholesterol clearly is not an essential dietary constituent. Human subjects and experimental animals maintained on cholesterol-free diets not only show relatively constant serum cholesterol levels but continue to excrete sterols in the feces. This indicates synthesis of cholesterol in the body, a process which Schoenheimer was able to demonstrate by careful balance studies in the rat.

There has been a great deal of speculation as to the precursors of cholesterol and its rate of synthesis in the body. Earlier theories postulated the direct formation of cholesterol from fatty acids and several schemes for this conversion were proposed but no adequate proof has been advanced for the formation of sterols directly from fatty acids. Plant sterols differ but slightly from cholesterol in their structure but they are not absorbed in the alimentary tract of animals.

Actually no real progress was made in elucidating the metabolism of cholesterol until the introduction of isotope technics, notably by Schoenheimer, Rittenberg and Bloch. If a constant concentration of heavy water is maintained in the body fluids of an animal, all synthetic reactions take place in a medium of D₂O and all compounds synthesized will contain deuterium. From a study of the uptake of heavy hydrogen it is possible to measure the rate of synthesis of the compound even if nothing is known of the actual chemical mechanism. Schoen-

⁶ FIESER, L. F. Chemistry of Natural Products Related to Phenanthrene. 2nd ed., pp. 111, 112. New York, 1937. Reinhold Pub. Corp.

heimer and Rittenberg made such rate studies with mice on a cholesterol-free diet. By sacrificing mice after different intervals, it was found that the deuterium content of the body cholesterol steadily increased until a maximum value was reached. From

analysis of the results it was calculated that half of the body cholesterol was destroyed and resynthesized in approximately thirty days. About 2 per cent of the cholesterol was replaced every day. Similar studies by Waelsch and Sperry showed that the cho-

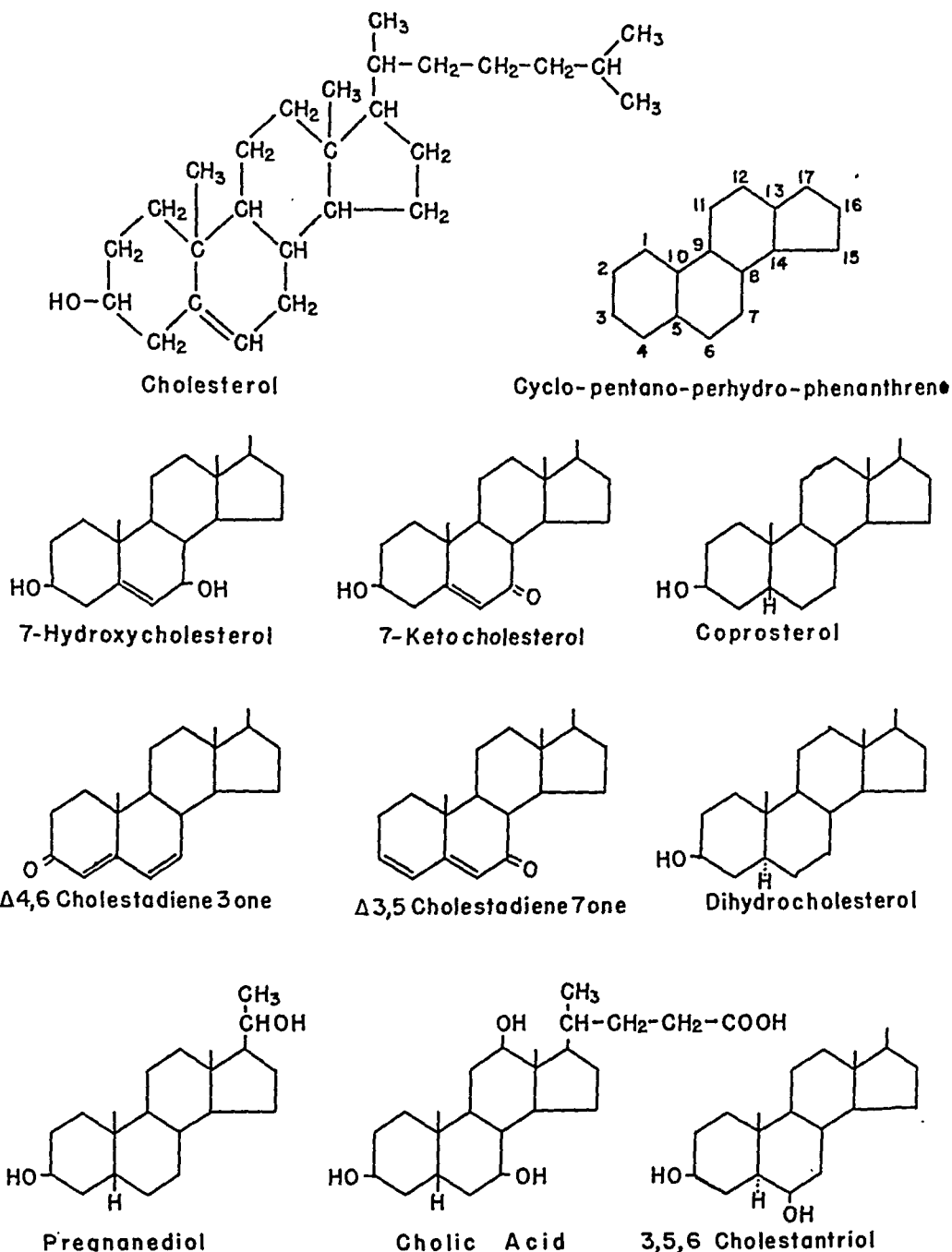


FIG. 4. Structural formulas of cholesterol and related compounds. The cyclopentano-perhydro-phenanthrene nucleus is common to all these compounds with the positions numbered as indicated. In all compounds the substituent groups at C_{10} , C_{13} and C_{17} are the same as in cholesterol unless otherwise indicated. Where C_5 is fully reduced, two stereoisomers arise and are differentiated by solid and broken lines. Erratum: The H attached to C_5 in the formula 3,5,6 cholestantriol should be an OH.

lesterol in the brain of adult mice differs from cholesterol elsewhere in that it is not replaced by newly synthesized cholesterol during the course of the experiment.

Schoenheimer and Rittenberg showed that after the mice have been on experiment for a long time the deuterium concentration in the cholesterol becomes equal to half that of the body water. This demonstrates that during the synthesis half of the hydrogen atoms of the compound are derived from water. A reasonable deduction is that cholesterol must be built up from compounds of low molecular weight. A search by the isotope technic finally revealed one precursor of cholesterol. Bloch and Rittenberg found that feeding of deuterio-acetate to rats results in the formation of deuterio-cholesterol. Acetate therefore is a precursor of cholesterol; but since acetate is not an important dietary component, it in turn must be synthesized. The major sources of acetate are the fatty acids and the ketogenic amino acids. However, since carbohydrates are readily converted into fats in the body, any dietary component may possibly act as a precursor of cholesterol. Bloch⁷ has recently reviewed current views as to the sources of acetic acid in the body and its general importance as a source of carbon atoms in the synthesis of larger molecules.

Bloch, Borek and Rittenberg studied the site of synthesis of cholesterol in the body by incubating tissue slices from different organs with heavy water, with deuterio-acetate, and with acetate containing deuterium in the methyl group and C¹³ in the carbonyl group. Synthesis of cholesterol could be demonstrated only in the liver slices. The rate of synthesis by the liver slices was high enough to warrant the deduction that cholesterol is formed principally in the liver. Recently, however, Chaikoff and co-workers made the interesting observation that adrenal cortical tissue also is capable of synthesis of cholesterol from acetate *in vitro*.

Little is known about the breakdown of

cholesterol in the body. It has been supposed that the ring system of the molecule is comparatively stable. However, now that it has been shown that the molecule can be built up from small molecules, we cannot eliminate the possibility that the ring system may also be degraded.

Isotope studies have shown that cholesterol is the mother substance of at least two related steroids. Suspensions of deuterio-cholesterol were injected into dogs. After collecting the bile over a three-day period the dogs were sacrificed and the organs analysed. Deuterio-cholic acid was isolated from the bile. The quantitative data indicated that most if not all of the cholic acid was derived from cholesterol. Analysis of the organs showed that the largest amount of the injected cholesterol had been deposited in the lungs and the liver. None was detected in the brain or spinal cord. The feeding of deuterio-cholesterol to a pregnant woman resulted in the excretion of deuterio-pregnandiol. This compound while not a sex hormone is generally believed to be a reduction product of the sex hormone progesterone. At present it is not possible to say whether or not other sex hormones are derived from cholesterol.

Additional studies of this kind are needed to clarify our understanding of cholesterol metabolism and its possible relation to arteriosclerosis. The work already reported has made it clear that controlling cholesterol intake may have very little effect upon the over-all cholesterol metabolism since the body can synthesize cholesterol from protein, fats and carbohydrates.

DR. DAVID RITTENBERG: Dr. Batchelor has reviewed our present knowledge of this subject very well. I should like to point out, however, that the experiments with deuterio-acetate account for less than half the carbon atoms in cholesterol. It appears therefore that other precursors must be involved. We have recently obtained evidence that administration of labeled acetone results in the formation of labeled cholesterol. This reaction occurs not only in the intact animal but also in surviving liver

⁷ BLOCH, K. The metabolism of acetic acid in animal tissues. *Physiol. Rev.*, 27: 594, 1945.

tissue. It is possible that acetone is the precursor of the methyl groups in the sterol.

DR. SEEGAL: With this background we might now turn to a closer examination of the problem of arteriosclerosis itself. For reasons already indicated it is difficult to attack the problem directly in man. Such progress as has been made stems largely from animal experiment. I have asked Dr. Kendall to review this field, with special reference to the work of his own group.

DR. FORREST E. KENDALL: Dr. Seegal has stressed the fact that arteriosclerosis cannot be adequately diagnosed and followed in man. Clinical investigation in this field has consisted largely of the collection of laboratory data in the hope that some relationship might be found between these data and a subsequent demonstration of arteriosclerosis. Since the disease process extends over a period of years and even decades and since exact information of what has taken place can be obtained only at the end of the process, clinical progress has necessarily been slow. Many attempts have therefore been made to reproduce and study the disease in experimental animals. Intimal lesions resembling those seen in man have been produced experimentally in the rabbit, chicken and dog by greatly increasing the serum cholesterol level.

In the rabbit intimal arteriosclerosis almost never occurs spontaneously but, as Anitschkow showed in 1913, addition of cholesterol to the diet of the rabbit results in the production of intimal arterial lesions. The extent of the lesions and the length of time required to produce them depend upon the degree of hypercholesterolemia. Anitschkow in 1932 reviewed the work up to that time and presented arguments for considering that the rabbit lesions are identical with those of human arteriosclerosis. However, Duff² and other investigators pointed out that: (1) The distribution of the lesions in rabbits is different from that seen in man in that the thoracic aorta and pulmonary arteries are the vessels most severely damaged and that lesions never occur in the cerebral vessels and are rare

in the peripheral and renal arteries and in the other branches of the abdominal aorta; (2) the lesions in rabbits resemble the early stages of arteriosclerosis in humans but the more advanced types of lesions do not develop; (3) cholesterol feeding does not result in significant hypercholesterolemia and arterial lesions in omnivorous animals such as the dog, cat, rat or monkey. It has therefore been argued that the lesions produced in the rabbit are simply the response of an herbivorous animal to a substance which is not normally present in its diet and for which it has no effective metabolic pathway.

In contrast to the rabbit, chickens and many other birds do have spontaneous arteriosclerosis. Intimal lesions are almost always found in the arteries of aged chickens. In distribution and morphology these lesions closely parallel those seen in man. The underlying cause of these spontaneous lesions in the chicken is as much of a mystery as is the cause of human arteriosclerosis. However, it has been shown that raising the serum cholesterol level in young cockerels either by feeding them cholesterol or by administering stilbestrol results in the premature development of arteriosclerosis.

The occurrence of spontaneous intimal lesions in dogs is rare but not unknown. It was as high as 5 per cent in some series of old dogs. Many attempts in the past to produce arteriosclerosis in dogs by feeding them large amounts of cholesterol failed and in no case could a sustained hypercholesterolemia be maintained. However, in a recent report from this laboratory⁸ it was demonstrated that if the function of the thyroid gland of dogs was modified by thiouracil administration, the feeding of cholesterol resulted in greatly elevated serum cholesterol levels. Maintenance of this hypercholesterolemia for a period of twelve to sixteen months resulted in lesions similar in distribution and morphologic characteristics to those seen in human

⁸ STEINER, A. and KENDALL, F. E. Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil. *Arch. Path.*, 42: 433, 1946.

arteriosclerosis. I would like to present this work in some detail.

Our first study involved four mongrel dogs. All of these animals were given thiouracil in doses starting at 0.5 Gm. and increasing to 1.2 Gm. per day. It was observed that from a control serum cholesterol level of 150 to 160 mg. per cent, the levels rose to 210 mg. per cent during the two months on thiouracil. At this point cholesterol was added to the diet of three of the dogs in the form of 10 Gm. of cholesterol in 40 cc. cottonseed oil daily. The serum cholesterol levels of these animals then rose progressively over the course of the next fourteen months to peaks of 932, 1,134 and 2,176 mg. per cent. During this time one dog had remained on thiouracil alone and showed a serum cholesterol level which averaged 284 mg. per cent. When the dogs were sacrificed after twelve to fourteen months of this hypercholesterolemia, the three cholesterol-fed animals showed arteriosclerotic lesions which were similar to human lesions in distribution and morphology. The dog which had received thiouracil without cholesterol showed no arterial lesions.

We have been able to repeat these results in young dogs of known age and antecedents. A group of four littermate mongrel dogs born in our laboratory was started on cholesterol feeding at the age of four months. This time the daily 10 Gm. of cholesterol was dissolved in ether, then applied to the dry diet of Spratt's meat fibrine dog cakes and the ether allowed to evaporate. This left the cholesterol well distributed throughout the food in finely divided form and obviated the high fat intake occasioned by the cottonseed oil used in our first series of dogs. Analysis of the feces indicated that from 60 to 80 per cent of this cholesterol was absorbed. During this cholesterol feeding period the serum cholesterol rose to 400 to 500 mg. per cent. After four weeks on cholesterol alone two of the dogs were in addition given thiouracil, starting with 0.8 Gm. per day and increasing finally to 1.2 Gm. per day. The other

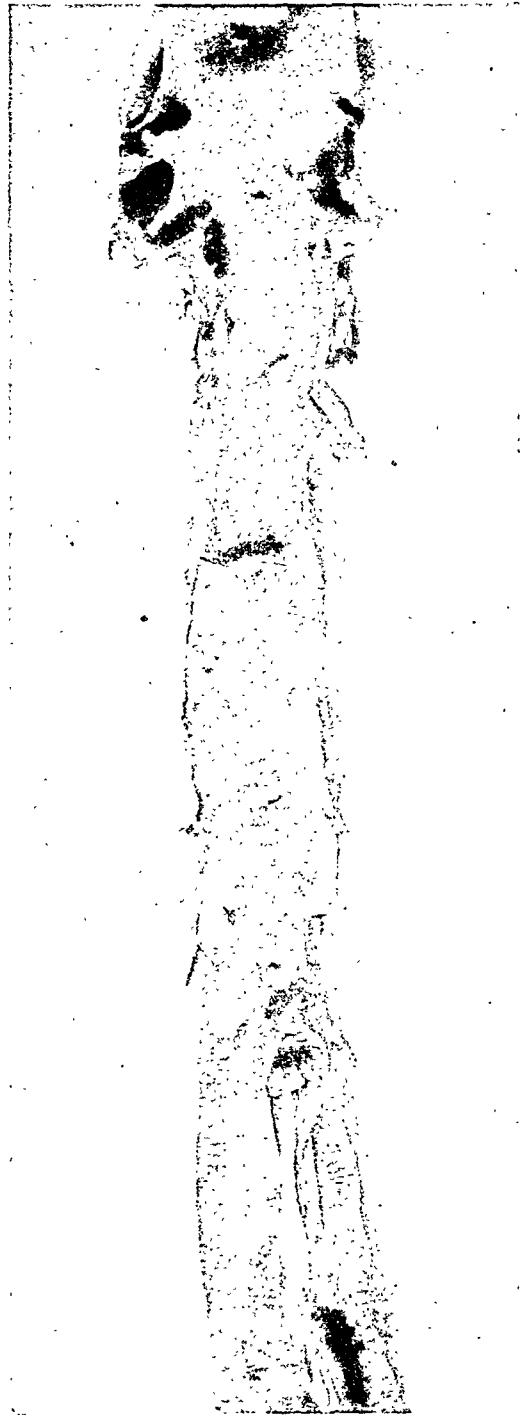


FIG. 5. Dog arteriosclerosis; abdominal aorta showing multiple intimal plaques which coalesce about the exit of the branches. The circular muscle bundles of the iliac arteries are accentuated by the plaques.

two dogs were kept on cholesterol but were given no thiouracil. The serum cholesterol level of the "cholesterol" dogs averaged 400 mg. per cent. The average levels of the

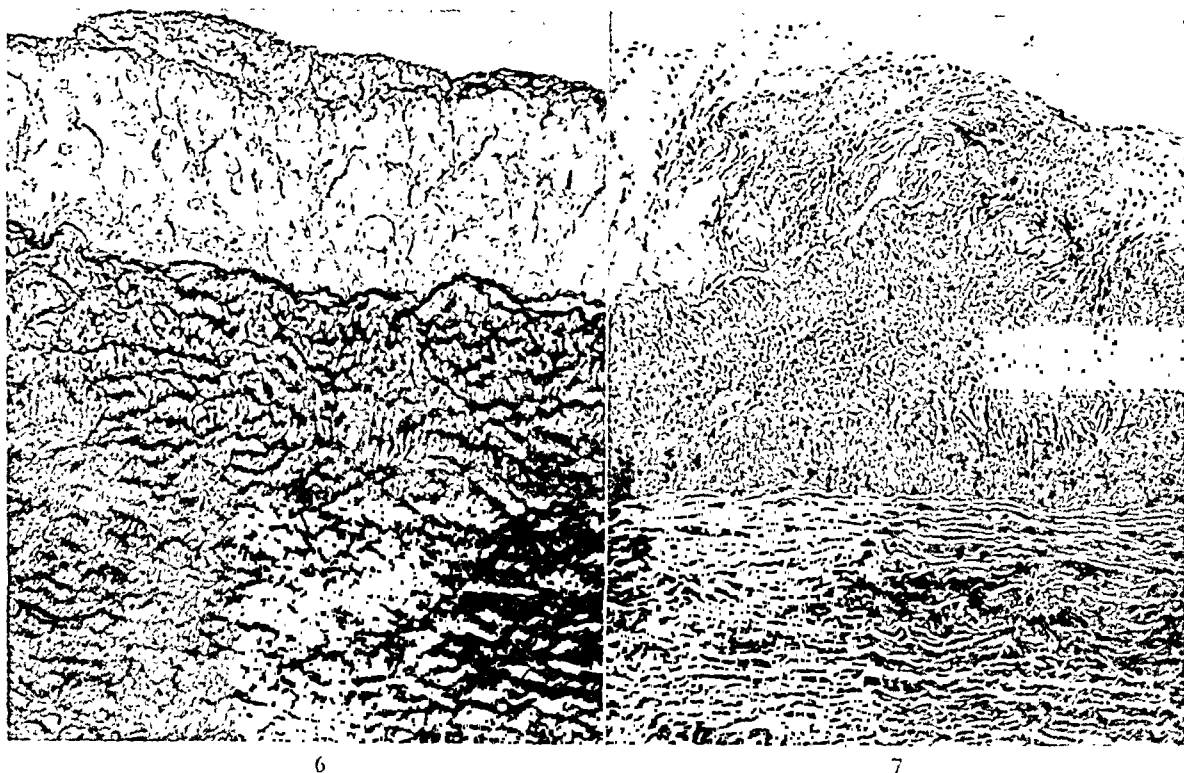


FIG. 6. Dog arteriosclerosis; an early lesion in the thoracic aorta. Two distinct layers of atheromatous deposits are apparent. The internal elastica is intact but lipid has infiltrated to the media beneath the plaque giving the upper portion a loose vacuolated appearance; elastic tissue stain, $\times 163$.

FIG. 7. Dog arteriosclerosis; iliac artery; a typical plaque with foam cells and fibrosis. Vacuolated spaces representing lipid appear in the media. The internal elastica is visible at the left but disappears beneath the fibrotic area of the plaque; hematoxylin and eosin stain, $\times 163$.

"cholesterol-thiouracil" dogs for the sixty weeks were 1,089 and 1,206 mg. per cent.

When the cholesterol-fed controls were sacrificed after seventy-two weeks, one showed no arterial lesions. The other dog, which had almost identical serum cholesterol levels, showed several fine, raised yellow streaks in its abdominal aorta. On microscopic section these were seen to consist of lipid depositions beneath the aortic intima, forming an early arteriosclerotic plaque.

Autopsy of the two "cholesterol-thiouracil" dogs after sixty weeks revealed extensive generalized arteriosclerosis in both animals. The lesions varied from small, pin-point, yellowish elevations of the intima to large, coalescing plaques. Lesions were most marked in the abdominal aorta and its branches. Figure 5 shows the gross appearance of one of these aortas, with the most advanced lesions in the abdominal

aorta and its branches. Lesions were also present in the thoracic aorta, iliac, femoral, coronary, innominate, thyroid, subclavian, mesenteric and renal arteries and in the sinus of Valsalva. For the first time cerebral lesions were found about the circle of Willis in both of these dogs. Microscopically, the lesions showed almost all of the features of human arteriosclerosis. Figure 6 shows an elastic tissue stain of an aortic lesion. This is an early lesion. The intima is raised with fat-laden foam cells. Some fat-laden cells are apparent in the media beneath the as yet intact internal elastica. A section of a typical iliac artery plaque (Fig. 7) shows the marked thickening of the intima with fibrosis and fat-laden cells penetrating into the media. The coronary arteries (Fig. 8) show arteriosclerotic lesions which replace much of the media, thicken the intima and narrow the lumen. In the larger artery you can see most of the morphologic



FIG. 8. Dog arteriosclerosis; coronary artery; showing many of the sequelae of human arteriosclerosis. The lumen is narrowed by diffuse atheromatous deposits. Within the plaques are hemorrhage, hyalinization and calcium. The media has been partially replaced by lipid deposits; hematoxylin and eosin stain, $\times 86$.

features of an advanced human lesion including hemorrhage within the plaque, hyalinization, and about the outer margin of the lesion a thin, bluish line of calcification. In the middle cerebral artery (Fig. 9) the lesion is apparently limited to the intima with considerable narrowing of the lumen. Such cerebral lesions were present in both of our last "cholesterol-thiouracil" dogs.

It is clear, then, that arteriosclerosis can be produced in an omnivorous mammal, the dog, by feeding cholesterol and thiouracil. The resultant lesions have the same anatomic distribution and sites of predilection as those in man, including involvement of coronary, renal and cerebral arteries. The dog lesions have most of the morphologic features of human arteriosclerosis, including hyalinization, hemorrhage and calcification. In no case thus far, however, has ulceration into the lumen of the artery been observed.

Thiouracil in the doses used does not itself lead to arterial lesions. In one instance early arteriosclerotic lesions developed following the feeding of 10 Gm. cholesterol



FIG. 9. Dog arteriosclerosis: middle cerebral artery. Intimal atheromatous deposits narrow the lumen. Fibrous tissue beneath the endothelium and at the edges of the larger plaque is encroaching upon the foam cells; hematoxylin and eosin stain, $\times 144$.

per day in a diet otherwise containing less than 5 per cent fat and without thiouracil.

Although our series of arteriosclerotic dogs is still too small to permit any positive correlation of the degree of hypercholesterolemia with the extent of the lesions, it is interesting to note that no lesions have been found in dogs in which the serum cholesterol level was less than 400 mg. per cent for twelve months. Above this level, without exception, the higher the serum level (over the 12- to 14-month period) the more extensive was the arteriosclerosis found at autopsy. Experiments are in progress to quantitate further the degree and duration of the hypercholesterolemia necessary for the production of arterial lesions.

STUDENT: I would like to ask how far it was necessary to depress the basal metabolic rate in the dogs that developed arteriosclerotic lesions on the combined cholesterol-thiouracil regimen.

DR. SEEGAL: Dr. Davidson has determined the basal metabolic rate in some of these dogs and can give us that information. I hope he will tell us about the methods he employed because determining the basal metabolic rate in dogs proved to be a more difficult feat than was anticipated.

DR. JACK D. DAVIDSON: The basal metabolic rate was not determined in the dog

experiments described by Dr. Kendall but they are currently being determined in a similar group of dogs receiving 1.2 Gm. thiouracil per day. The basal metabolism is estimated by the use of a standard clinical type of Sanborn machine adapted to the dog by the use of a pneumatic cushioned muzzle mask which gives an air-tight seal when applied to the shaven and lubricated muzzles. Light sodium pentobarbital hypnosis is used to obviate the long period of training otherwise required. This light hypnosis has been shown by Cavett and by Galvão to have no perceptible effect upon the basal metabolic rate of the dog. In our animals 13 mg. of sodium pentobarbital per Kg. body weight given intravenously causes hypnosis which is light enough to be interrupted by any painful stimuli and which terminates with the dog spontaneously lifting his head after twenty to forty minutes. Since there is considerable disagreement as to standard basal metabolic rates for dogs, due to poor correlation of caloric production with physical measurements and the confusion caused by species differences and different types of hair, we have used the results of control Sanborn measurements on each dog prior to thiouracil feeding as the normal standard or "0" per cent for that animal. Subsequent variation has then been expressed as a percentage of this normal value for the given dog. On this basis the animals on this experiment have shown basal metabolic rates which are -15 to -20 per cent. The animals do not look or act myxedematous and show normal growth; but their tolerance to sodium pentobarbital has definitely diminished as their basal metabolic rates declined, and their tolerance to cold is below normal as shown by shivering under conditions that do not cause normal dogs to shiver.

STUDENT: Have you tried to produce arteriosclerosis in rats or mice?

DR. KENDALL: We have tried to produce lesions in rats by combined cholesterol-thiouracil feeding but failed to produce sustained hypercholesterolemia of significant

degree and no atheromas were apparent either grossly or microscopically.

STUDENT: Have you any explanation for these species differences?

DR. KENDALL: No.

DR. KENNETH B. TURNER: There are interesting differences in the response to cholesterol feeding not only between animals of different species but also between different animals of the same species. For example, in experiments carried out some years ago we found marked individual differences among our rabbits with respect to the maximal level of cholesterol in the blood after feeding the same amount of cholesterol. In one animal it might never rise above 300 mg. per cent while in another receiving the same amount of cholesterol over the same period the level might rise to 1,200 or 1,300 mg. per cent. Eventually, however, the level of cholesterol in the blood of each animal reaches an irregular plateau. This would seem to indicate that the animals somehow acquire the ability to metabolize or excrete the large amounts of cholesterol administered and thus achieve a state of equilibrium. An occasional rabbit displays from the start surprising capacity to handle exogenous cholesterol so that after several months of feeding only a slight elevation of the blood cholesterol has occurred. This so-called "resistance" is abolished by thyroidectomy. In the otherwise normal rabbit thyroidectomy results in only a slight rise in serum cholesterol; but when performed in a cholesterol-fed but "resistant" rabbit, there is prompt disappearance of the "resistance," with development of marked hypercholesterolemia.

The experience with rabbits in the production of atherosclerosis by cholesterol feeding coincides with that indicated by Dr. Kendall in dogs. Atherosclerosis does not occur in the rabbit without antecedent elevation of the blood cholesterol; to this there are no exceptions provided one excludes medial sclerosis, a quite distinct lesion which may occur "spontaneously." Hypercholesterolemia without atherosclero-

sis, on the other hand, is observed in cholesterol-fed rabbits although infrequently.

When a rabbit fed cholesterol for a sufficient period of time is autopsied, certain lesions in addition to the atheromatous changes in the aorta are obvious upon gross

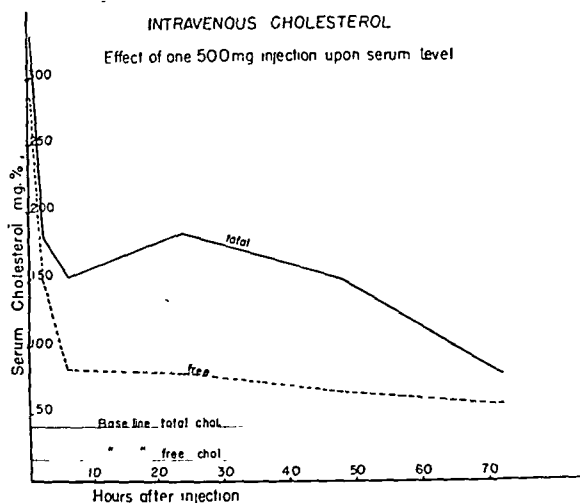


FIG. 10. Serum cholesterol levels in the rabbit after intravenous injection of cholesterol suspension. Note the rise in total cholesterol at the twenty-four-hour interval while the free cholesterol is unchanged. The rise is due entirely to an increase in cholesterol esters.

examination. There is a fatty liver, the adrenals are large and there are fatty deposits in the spleen and kidneys. This simultaneous development of lipoidosis has been cited as a point of dissimilarity between the atherosclerosis of rabbit and man. However, if cholesterol feeding is discontinued after a sufficient period of hypercholesterolemia, the blood cholesterol gradually drops to normal levels; and if the animals are sacrificed at this time, the gross findings at autopsy may be quite different. The atheromas persist but the visceral lesions are slight or absent. It should be emphasized that in this situation one finds atherosclerosis associated with normal levels of cholesterol in the blood at the time the animal is sacrificed.

DR. BEVANS: It might be worth pointing out that in such rabbits, although lipoid is continually absorbed from the aortic lesions, plaques may be discernible for as long as three years after cholesterol feeding has ceased and the serum cholesterol has returned to base line levels.

DR. SEEGAL: Because of uncertainties in the absorption of the cholesterol fed these experimental animals by mouth, investigators have long been interested in producing atherosclerosis by intravenous injection of cholesterol suspensions. These attempts were unsuccessful until about two years ago when Dr. Kendall prepared an emulsion of 2.5 per cent cholesterol stabilized in 0.5 per cent sodium stearate and found that this suspension could be injected into the ear veins of rabbits without difficulty. It has been possible in this way to produce lesions indistinguishable in appearance and distribution from those of animals fed similar amounts of cholesterol over the same period of time. The results have been especially illuminating in clarifying the morphologic sequence of events in the genesis of arteriosclerotic plaques and I have asked Dr. Bevans to tell us about these experiments.

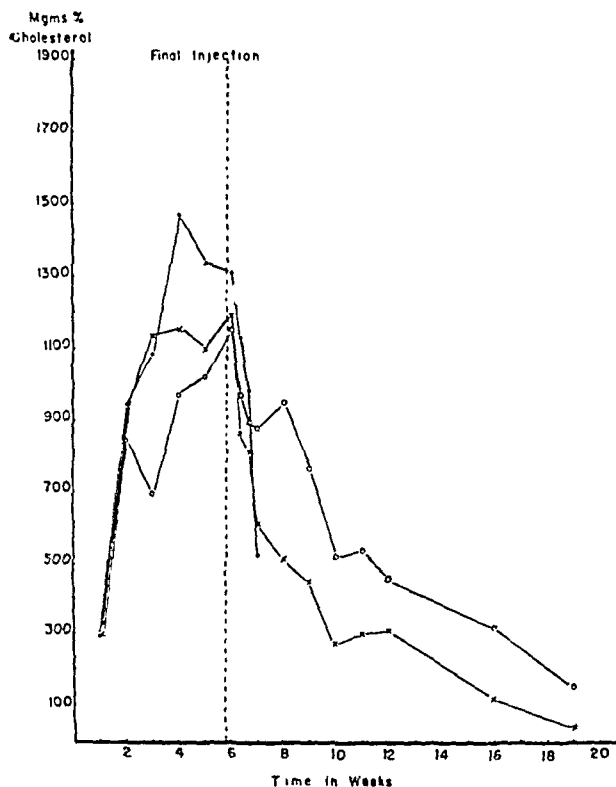
DR. BEVANS: We have followed the blood levels and the development of these lesions and I will describe some of our results. After a single injection of 0.5 Gm. of colloidal cholesterol, blood levels were determined at intervals of ten minutes, six hours, twenty-four hours and forty-eight hours. A sample curve is shown in Figure 10. It is apparent that the secondary rise in total cholesterol which consistently occurs at the end of twenty-four hours is due to a rise in the ester fraction and not in the free cholesterol. This suggests that the injected cholesterol is cleared from the blood and then slowly returned after esterification. A close relationship between the chemical and histologic findings exists since the amount of lipoid in the parenchymal cells of the liver reaches its peak at twenty-four hours and decreases from that time on. At the end of six days the serum cholesterol returns to base line values. It is possible to repeat the curve in the same animal many times.

When five injections a week of 0.5 Gm. of cholesterol each were given, the serum cholesterol levels attained were of the same order as those observed in rabbits fed the

same amount of cholesterol in their diet. (Fig. 11.) It will be noted also that the rate of disappearance is approximately the same in each group. As early as three hours after the first injection of 0.5 Gm. of cholesterol, lipid is visible within the intima of the

an occasional intimal endothelial cell of the small vessels. That the lipid material observed in the intima does not enter via the vasa vasorum can readily be seen in those areas where the intimal accumulation is far removed from these vessels.

14.5 GM. CHOLESTEROL I.V. IN 36 DAYS



FED 24.5 GM. CHOLESTEROL IN 49 DAYS

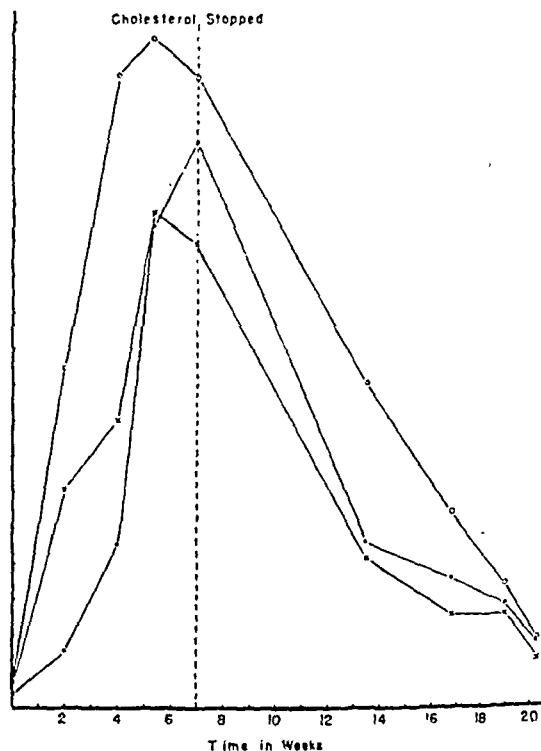


FIG. 11. Comparison of serum cholesterol levels after injection or feeding of cholesterol in rabbits. Note that the animals were fed for forty-nine days while the other group was injected for thirty-six days. At the thirty-six-day interval the serum cholesterol levels are similar.

aorta. It first appears within the endothelial cells which are swollen and prominent. At the end of twenty-four hours more lipid is visible in the endothelial cells and has spread to the intercellular substance. No intimal proliferation has occurred. At seventy-two hours less lipid is present in the intima but cellular proliferation is evident. By this time lipid has penetrated the internal elastica and the upper layers of the media. The endothelial cells are foamy. During these early phases the vasa vasorum of the outer media and adventitia are diffusely stained with lipid. This is no longer apparent after the seventy-two-hour period except for a few sudanophilic droplets in

As the interval after the single injection lengthens, less and less lipid is present within the intima but the proliferation of intimal cells continues to be present for at least two months. At the end of six months all lipid has disappeared and no intimal proliferation can be found.

When rabbits are given twelve daily injections of 0.5 Gm. of the cholesterol suspension, the first gross lesions can be identified in the ascending aorta. Microscopically, these lesions are well developed atheromatous plaques with abundant lipid. Sudanophilic material can be followed through the media into the peri-aortic tissues. (Fig. 12.) When rabbits are given



FIG. 12. Plaque in intima of ascending aorta noted grossly after twelve daily injections totaling 6 Gm. of colloidal cholesterol. The rabbit was sacrificed one month after the last injection. Lipid can be traced through the media and has collected in the adventitial and peri-aortic connective tissue; Sudan IV stain, $\times 125$.

thirty-six injections over a six-week period, the lesions are much larger and more numerous. As has been stated before they are indistinguishable in number, appearance and distribution from those seen in animals fed the same amount of cholesterol (18 Gm.) over the same period of time. Whether these animals are sacrificed immediately or six months later makes little difference in the appearance of the lesions.

Lipid found elsewhere in the organs is in proportion to the amount injected. Within three hours after a single injection, small amounts are found in the Kupffer cells of the liver but very little in the parenchymal cells. The sudanophilic droplets are more numerous after twenty-four hours when they are present also in the endothelial cells of the portal veins and stain the entire wall of the vein diffusely. Some of the lipid has migrated to the perivascular tissue and appears in the connective tissue cells. At three hours there is little lipid in the parenchymal cells but this increases up to twenty-four hours. Following this there is a decline until at the end of a month only small droplets remain in the Kupffer cells. About the same amount is present at the end of six months. In the kidney, at the end of twenty-four hours following a single injection, the blood vessel walls and glomeru-

lar capillaries are flooded with sudanophilic material. Numerous droplets are present in the tubular epithelium. At the end of a week glomeruli no longer contain lipid and only small amounts remain in the tubular epithelium. In the lungs and spleen a similar flooding of endothelial cells of the large vessels and walls of the capillaries is observed. Despite the large quantities of emulsion injected we have never observed large pulmonary emboli.

As larger amounts of cholesterol are injected, more and more lipid accumulates and remains for longer periods. It is evident that cholesterol is taken up through the body of the rabbit by the reticuloendothelial system but it is also evident that it remains in the intima of the aorta long after it is cleared elsewhere.

Since lipid can be detected in the intima of the aorta within three hours following injection of cholesterol suspension, these experiments suggest direct penetration of the intact endothelium by lipid in the development of atheromatous plaques. It would be difficult to reconcile these observations with Leary's hypothesis that fat-laden Kupffer cells of the liver migrate to the wall of the aorta to form the nidus of an atheroma.

DR. SEEGAL: It is clear that the experimental production of arteriosclerosis in animals has already thrown much light upon the problem of arteriosclerosis in man. This would be even more evident if we were able to present the work of other investigators in this field but time does not permit. We must go on to consider the clinical aspects of the problem. Dr. Steiner has for some years been working on the relationship of human arteriosclerosis to cholesterol metabolism and I have asked him to summarize his experience.

DR. ALFRED STEINER: The range of serum cholesterol values in normal human subjects is wide. The two technics most widely used are those of Bloor, in which the range of normal cholesterol varies from 175 to 300 mg. per 100 cc., and the method of Schoenheimer and Sperry, in which the range

varies from 150 to 275 mg. per 100 cc. The method of Schoenheimer and Sperry is considered to be more accurate although it is technically difficult and requires considerable facility before reproducible results are obtained. The ratio of ester to free cholesterol is constant, approximately 3 to 1.

In a study with Dr. K. B. Turner it was demonstrated that in a group of relatively normal persons the individual serum cholesterol levels remain quite constant from hour to hour, day to day and month to month during the period of a year. The deviation from the mean cholesterol level for each patient was less than 10 per cent.

In well documented coronary arteriosclerosis the results of serum cholesterol determinations have given inconclusive results. Several reports record an elevation of serum cholesterol while others do not. In our own studies frequent consecutive determinations of serum cholesterol for periods up to two years were made in fifteen patients with coronary arteriosclerosis. Thirteen of these patients had had a typical coronary thrombosis; the remaining two individuals had angina pectoris with a positive anoxemia test for coronary insufficiency. The patients were not included in this study until at least six weeks had elapsed since the onset of the myocardial infarction. A total of 914 serum cholesterol determinations were made, 572 on the patients with coronary arteriosclerosis and 342 in the normal individuals. The average serum cholesterol of the patients with coronary arteriosclerosis was found to vary from 308 to 499 mg. %, with a mean for the group of 355 mg. %; the standard deviation for the patients was 24.8. In contrast the average serum cholesterol values for each of fifteen relatively normal individuals varied from 214 to 334 mg. %, with a mean average of 254 mg. % for the group. The fluctuations of the serum cholesterol, as measured by the standard deviation, for the normal subjects averaged 8.7, about one-third of that of the patients with coronary arteriosclerosis.

Although statistically these results are significant, it was believed desirable to have serum cholesterol determinations on a larger group of patients. For this reason a single serum cholesterol determination was made in fifty additional patients with coronary arteriosclerosis and in fifty additional normal persons of the same age group. The average serum cholesterol value for the second group of patients with coronary arteriosclerosis was 336 mg. %, in contrast to 236 mg. % for the control subjects. These results confirmed the previous observations.

Since these studies were reported, Lerman and White found that twenty-two of twenty-eight patients with coronary arteriosclerosis under the age of forty had an elevation of serum cholesterol. Boas also has reported that an elevated serum cholesterol is a frequent finding in patients with coronary arteriosclerosis and furthermore in members of the families of these individuals.

In summary, the serum cholesterol level of patients with overt coronary arteriosclerosis is significantly higher than that of normal subjects of the same age group. Moreover, the serum cholesterol level of patients with coronary sclerosis fluctuates much more widely than in the normal subject.

A number of possible factors that might influence the serum cholesterol levels in human subjects have been studied. The administration of potassium iodide, a favorite of the older clinicians in the treatment of arteriosclerosis, has been shown to have no effect on the serum cholesterol level. Four and one-half grains of thyroid extract daily, however, resulted in a lowering of the serum cholesterol level approximately 90 mg. per cent in four to five weeks, associated with an increase in the basal metabolic rate of approximately 21 per cent. The post-thyroid period was of interest in that the serum cholesterol level overshot the normal level and remained elevated for two to four weeks. The feeding of soya lecithin results in a temporary lowering of serum cholesterol in normal individuals as well as in those with hypercholesterolemia associated with xanthomatosis.

The effect of an infection, pneumonia, on the serum cholesterol level was studied. Serum cholesterol estimations were made at frequent intervals during and subsequent to pneumonia in nineteen patients. The presence of *hybocholesterolemia* during the acute phase of the pneumonia was confirmed. It was further noted, however, that a subsequent *hypercholesterolemia* associated with wide fluctuations occurred during convalescence before the characteristic stable individual serum cholesterol level was re-established. In the patients studied the increase in serum cholesterol over the normal level varied from 20 to 250 mg. per cent, averaging 82 mg. per cent. The duration of the elevated and inconstant serum cholesterol values averaged fifty-two days. It is conceivable that such a period of transient *hypercholesterolemia* might lead to deposits of cholesterol in the arteries.

The effect of diet on serum cholesterol would appear to have considerable significance in view of some of the experiments described today. Leary, and more recently Dock, have advocated the restriction of dietary cholesterol so as to prevent or retard the development of arteriosclerosis. The rationale for this suggestion was based chiefly on the experimental arteriosclerosis produced by excess feeding of cholesterol. However, there are other data which tend to suggest that diet has an important bearing on the development of arteriosclerosis. In China, Okinawa and Costa Rica, where poor nutrition is prevalent, a low incidence of arteriosclerosis has been reported. The diet in these countries is characteristically low in cholesterol, protein and calories and is made up chiefly of carbohydrates of vegetable origin.

The tendency for individuals who are obese to succumb more commonly to sequelae of arteriosclerosis and coronary or cerebral occlusion has been noted by analysis of statistics by life insurance companies. French and Dock stated that seventy-three of eighty young soldiers dying of coronary arteriosclerosis had some degree of obesity.

It was therefore considered of interest to determine the effect of diets rich or poor in dietary cholesterol on the serum cholesterol level. In the first phase of this study the response of the serum cholesterol of thirty-five patients, with various diseases, to a single meal rich in fat and cholesterol was determined. The method of study was as follows: blood for analysis was taken at 8 A.M. with the patient in the fasting state. Breakfast consisted of fruits, two eggs, buttered toast, coffee and 200 cc. of milk to which 20 Gm. of cholesterol had been added. Dinner and supper were served at the usual hours. Additional blood samples were taken at 10 A.M., noon, 4 P.M. and 8 A.M. the following day. The results showed clearly that little or no change in the serum cholesterol occurred during the course of twenty-four hours, regardless of the feeding of a large amount of cholesterol.

In the second phase of this study nine individuals were placed on diets high or low in fat and cholesterol. They were first given a diet containing 300 Gm. of fat for six weeks and then without interruption placed on a diet containing less than 50 Gm. of fat. In five of the nine patients there was no increase in total serum cholesterol during the period of high fat feeding. In four cases a slight rise seemed to occur. Three of the patients subsequently were placed on the high fat diet for a second period but this time 10 Gm. of cholesterol in 200 cc. of milk was added to the regimen. No significant change resulted in the serum cholesterol levels.

The serum cholesterol levels of the patients on a low fat diet were no different from those observed during the control period.

This study has recently been repeated in four patients with coronary arteriosclerosis. After an initial control period the patients were given 100 Gm. of egg-yolk powder (roughly the equivalent of twelve egg yolks) containing 3 per cent cholesterol daily for six weeks. At the end of this time the diet was changed to one low in cholesterol (butter, cream, egg yolk and fatty meats

were excluded) for six additional weeks. Only slight increases in the serum cholesterol levels were found during the egg-yolk feeding period. It was possible in this experiment to estimate the quantity of cholesterol actually absorbed and metabolized by determining the amount of sterol excreted in the stool. No significant differences in the sterol excretion occurred during initial control and high or low fat and cholesterol diet periods. It can therefore be assumed that the dietary cholesterol was absorbed and either metabolized or laid down in the tissues. With the serum cholesterol and fecal sterol content essentially unchanged, one might infer that the mechanism of cholesterol turnover in the body is very active and able to handle large amounts of exogenous cholesterol. If this were not so, a marked elevation of serum cholesterol would be expected on a high cholesterol diet and, conversely, a fall in the serum cholesterol on a low cholesterol diet. Further studies of this problem by the isotope technic are indicated.

In the third phase of the effect of diet on serum cholesterol, ten patients with well documented episodes of coronary thrombosis were placed on a low cholesterol diet for periods from four to fourteen months. Butter, egg-yolk, cream and fatty meats were excluded from the diet during the low cholesterol regimen. Oleomargarine, a vegetable fat, was allowed. The patients were followed in the out-patient department so strict adherence to the diet may not have been observed; however, all the patients were most cooperative. Serum cholesterol determinations were made at intervals of two weeks or at monthly intervals. Preliminary results of this study indicate that the serum cholesterol levels of five of the ten patients were lower than those observed in the initial regular diet period. Considerable fluctuations of the serum cholesterol level occurred during the period of regular diet but seemed to be less variable during the low cholesterol diet period. It was not possible to judge adequately whether this

low cholesterol ingestion resulted in any change in the clinical status of the patients.

The recent demonstration by Rittenberg and his co-workers that cholesterol can be synthesized in the body from acetate—a substance formed in the metabolism of fat and possibly from glucose and protein—is pertinent to the problem of reduced cholesterol intake. If the body synthesizes excessive amounts of cholesterol, the restriction of dietary cholesterol intake would be of little avail. However, the overburdening of an already disturbed cholesterol metabolism by excessive cholesterol ingestion might be harmful. Further studies are necessary before a final evaluation of this problem can be made.

DOCTOR: Arteriosclerosis is frequently found in subjects who have serum cholesterol levels within the normal range and who have no history of recognized hypercholesterolemia in the past or any disease associated with hypercholesterolemia. They also have normal basal metabolic rates. Production of arteriosclerosis in animals in the experiments described by Dr. Kendall, however, required the sustained maintenance of marked hypercholesterolemia over long periods by instituting experimental conditions which so far as we know do not obtain in most clinical cases of arteriosclerosis. This raises the question in my mind as to how relevant the animal work is to the clinical problem of arteriosclerosis.

DR. KENDALL: The great resemblance between the lesions seen in clinical arteriosclerosis and those produced experimentally, particularly in the dog, leads us to believe that they are fundamentally alike. The failure to find a history of hypercholesterolemia in much of the clinical material suggests that it would be well to look beyond the high serum cholesterol levels in the experimental animals for the real cause of arteriosclerosis. It is possible that initiation of the lesion in both experimental animals and in human beings is not due to high cholesterol levels *per se* but to the presence of some abnormal

substance related to cholesterol. Although various oxidation products of cholesterol which may be intermediate compounds in its metabolism have been isolated from lesions of human aortas, very little is known about the role they may play in arteriosclerosis. Our laboratory has started an investigation of the physiologic significance of some of these compounds but all such work is seriously hampered by the inadequacy of available information concerning the intermediary metabolism of cholesterol, the way it is built up and broken down in the body. Further extension of isotope technics to obtain this fundamental information is urgently needed.

Another point which may be relevant to this discussion is the fact that the cholesterol of the serum is for the most part not in true solution but in colloidal suspension stabilized by the other lipids and the proteins of the serum. Normally only a small portion of this cholesterol can be extracted from the serum with organic solvents. In hypercholesterolemia occurring both in human beings and in experimental animals a large part of the cholesterol can be extracted. There has been a change in the physical state as well as in the amount of cholesterol present. It may develop that this change in physical state is one of the factors responsible for the development of atherosclerosis.

DR. STEINER: I do not think that the finding of arteriosclerosis in individuals who have had one or two casual serum cholesterol determinations within the normal range, a normal B.M.R. on one or more occasion, and who have not had one of the usual diseases associated with hypercholesterolemia (poorly controlled diabetes, myxedema, chronic nephritis or xanthomatosis), invalidates the significance of cholesterol in arteriosclerosis. That the serum cholesterol in relatively normal persons ordinarily remains quite constant so far as we know (the longest available study of serum cholesterol levels in normal subjects did not extend beyond a two-year period) does not rule out the possibility that periods

of hypercholesterolemia as well as of instability of the serum lipids may occur in the lifetime of some individuals. Certainly the demonstration that following an acute infection such as pneumonia the serum cholesterol level, after a period of hypocholesterolemia during the febrile phase, becomes elevated and extremely labile for periods up to three to six months, is a specific example of one of the factors influencing the serum cholesterol pattern during the lifetime of an individual. The serum cholesterol pattern may also be altered by other conditions, such as endocrine and dietary factors. It is quite possible that deposition of cholesterol in the walls of arteries may occur during such transitory periods of hypercholesterolemia. It would certainly seem significant that in all of the usual diseases that are associated with widespread and premature arteriosclerosis an elevation of serum cholesterol has been found, providing the study is adequate and carried on over a sufficiently long period. The fact that arteriosclerosis occurs in patients who have not been found to have elevated serum cholesterol levels may indicate only that our data are incomplete.

Another factor to be considered is the wide range of the normal serum cholesterol. If one individual's serum cholesterol ordinarily is 160 mg./100 cc. and is then increased to 250 mg., still a normal figure, I think we would have to say that this alteration was a significant one, and might be associated with infiltration of cholesterol into the tissues.

DOCTOR: Have you gotten any leads from the animal work that could be applied to the clinical problem of preventing or minimizing arteriosclerotic lesions in man?

DR. STEINER: Of course the ultimate aim of the animal work is just that. At present we are building up a large dog colony for the purpose of standardizing the conditions necessary to induce arteriosclerosis in dogs so that we can systematically test out the various possibilities in prevention of the lesions under adequately controlled conditions. Experiments with lipotropic agents

such as choline, which appears to have a preventative effect in rabbit arteriosclerosis,⁹ have already been extended to dogs but we are not yet able to give you any results. In the meantime we are continuing our clinical observations; our attempts to lower serum cholesterol levels particularly in subjects with coronary sclerosis by dietary measures. As we learn more about the dietary precursors of cholesterol in man and about the intermediary metabolism of cholesterol, we can direct these efforts more intelligently.

In any event, with the realization that arteriosclerosis is not an inevitable concomitant of aging but may be due to factors that can be controlled, investigation in this field has become more aggressive. We believe that sufficient progress has been made to justify further intensive efforts to prevent or minimize arteriosclerosis in man.

SUMMARY

DR. ALEXANDER B. GUTMAN: In view of the fact that arteriosclerosis in one or another of its complications and sequelae is responsible for more disability and death than any other disorder, it is surprising how little has been discovered concerning its causes, natural history, prevention and treatment. This has been due in large part to the general attitude of apathetic acceptance of arteriosclerosis as an inevitable consequence of aging. Moreover, such efforts as have been made to attack the clinical problem have been largely frustrated by inadequate methods of diagnosis except upon presumptive evidence or by the indications of late complications; the impossibility of quantitation of arteriosclerotic lesions during life; and the difficulty in distinguishing clinically between intimal and medial sclerosis, two distinct abnormalities.

In recent years a more aggressive attitude toward the problem of arteriosclerosis has evolved. This has, in large part, grown out of the successful production of atherosclerosis

in experimental animals, first in rabbits by Anitschkow, more recently in guinea pigs, chickens and dogs; in the dog (like man, an omnivorous mammal) the lesions produced are reasonable facsimiles of human arteriosclerosis as regards morphology, distribution and sites of predilection. The experimental reproduction of these lesions in young animals has encouraged the view that human arteriosclerosis may be due to factors that can be controlled.

Experimental atherosclerosis is produced by the administration of large amounts of cholesterol with consequent marked hypercholesterolemia (in the case of the dog it has been necessary also to depress thyroid function with thiouracil). This has focused attention upon the possible role of cholesterol in the pathogenesis of human arteriosclerosis. There are other reasons for this special interest in cholesterol: (1) In human arteriosclerosis the earliest detectable lesions are deposits of lipids in the intima. Chemical examination of the lipids obtained from arteriosclerotic human aortas has disclosed that cholesterol constitutes 40 to 65 per cent of the phospholipid-free fat content; in addition there are small amounts of at least four oxidation products of cholesterol and one reduction product. (2) Arteriosclerosis not infrequently develops prematurely and with great severity in such diverse diseases as poorly controlled diabetes mellitus, xanthomatosis, nephrosis and myxedema which have in common a marked increase in the blood lipids, particularly cholesterol. It has therefore seemed justifiable to limit this clinic largely to a consideration of cholesterol and its derivatives, referring to the reviews of Cowdry,¹ Duff,² Winternitz,³ Hueper⁴ and a recent Biological Symposium⁵ for a more comprehensive discussion of arteriosclerosis. Another excellent general review of arteriosclerosis, by Gubner, will be found in the review section of this issue of the American Journal of Medicine.

Cholesterol is a sterol, quantitatively by far the most important animal sterol and almost universally distributed in animal

⁹ STEINER, A. Effect of choline in the prevention of experimental aortic atherosclerosis. *Arch. Path.*, 45: 327, 1948.

tissues. Its function, however, is not known except insofar as it serves as a precursor of related physiologically active sterols. Part of the cholesterol in the body is absorbed from the preformed cholesterol of the diet but cholesterol is not an essential dietary constituent since, as is now clear, it can readily be synthesized by the body. Isotope technics have recently disclosed that acetate is an important precursor of cholesterol and that acetone is probably a source of the methyl groups. Neither acetate nor acetone as such are common constituents of the diet but large amounts are formed in the metabolism of fatty acids and ketogenic amino acids. Moreover, since carbohydrates are readily converted into fats in the body, it would appear that any dietary constituent may act as a precursor of cholesterol. This recent realization has important implications in attempts to control human arteriosclerosis by dietary measures.

Much of the remainder of this Clinic was devoted to a detailed presentation of the experimental production of atherosclerosis in dogs and rabbits by a group at the Columbia Research Service at Goldwater Memorial Hospital. Lesions were produced in young dogs by feeding 10 Gm. cholesterol daily in a standard diet otherwise containing less than 5 per cent fat, and simultaneously giving sufficient thiouracil to reduce the basal metabolic rate to about -15 to -20 per cent as compared with the control level. This regimen was maintained for about a year during which time marked hypercholesterolemia (average levels in excess of 1,000 mg. per cent) persisted. At necropsy extensive and advanced arteriosclerosis was found in these young dogs, including involvement of the aorta, coronary, renal and cerebral arteries. The fidelity with which arteriosclerosis in man was reproduced is evident from the photomicrographs which illustrate extension into the media, hyalinization, hemorrhage and calcification although no ulceration into the lumen of the artery has yet been observed.

The rabbit experiments described are of interest because they represent the first

successful attempt to produce atheromatosis by intravenous injection of stable cholesterol emulsions, specifically of 2.5 per cent cholesterol stabilized in 0.5 per cent sodium stearate. The results of this technic have shed much light upon the morphologic sequence of events in the genesis of arteriosclerotic plaques. Upon injection the cholesterol is rapidly taken up by the cells of the reticuloendothelial system throughout the body. Particularly large amounts of lipid appear in the liver, first in the Kupffer cells, then in the parenchymal cells from which it gradually disappears, probably after esterification and other metabolic changes have been effected. In the intima of the aorta, lipid can be detected within three hours of injection, suggesting direct penetration of the intact endothelium by the lipid. But whereas the lipid eventually disappears from most tissues without leaving a recognizable trace or scar, its appearance in the intima initiates a characteristic sequence of tissue reactions resulting in what we designate an atheromatous plaque, which persists for a long time. These facts have implications of interest in human arteriosclerosis.

Impressive though these experimental results are, it must be recognized that they are produced under conditions which have no counterpart in human arteriosclerosis. The amounts of cholesterol fed or injected are enormous relative to human dietary consumption of cholesterol; and in the dogs the basal metabolic rate must be reduced well below that of most clinical cases of arteriosclerosis. Marked and sustained hypercholesterolemia was a *sine qua non* in the experiments described whereas arteriosclerosis occurs frequently in human subjects with serum cholesterol levels within the normal range and with no history of recognized hypercholesterolemia in the past or any disease associated with hypercholesterolemia. It may therefore be hazardous to draw too literal an analogy between the mechanisms of experimental and clinical arteriosclerosis.

The differences, however, may well be quantitative rather than qualitative. It is evident that there are important species differences with regard to effective metabolic pathways for cholesterol. Man is predisposed to arteriosclerosis, to judge by the frequency of human arteriosclerosis as compared with the uncommon "spontaneous" occurrence of intimal atheromatosis in old rabbits and dogs. It may well be that the factors operating in experimental cholesterol atheromatosis in the rabbit and dog (and these are deliberately intensified to accelerate the production of maximal lesions) are needed in much lesser degree to provoke arteriosclerosis in man; and in some subjects specific abnormalities in lipid metabolism may accentuate the predisposition to arteriosclerosis. It is not unlikely that many people do have transitory periods of absolute or relative hypercholesterolemia which remain unrecognized and these may suffice to initiate aortic lesions which leave permanent scars. There is a distinct possibility that not cholesterol itself but some substance related to cholesterol is immediately responsible for the initiation of aortic lesions, a possibility now under investigation despite the difficulties arising from our very imperfect knowledge of the intermediary metabolism of cholesterol. In any event the evidence relating arteriosclerosis to a disordered cholesterol metabolism is too suggestive to be ignored.

The direct attack upon arteriosclerosis as it occurs in man is still in the exploratory stage. As there is no way to quantitate intimal atheromatosis and, therefore, to judge the effects of prophylactic and therapeutic agents, it has been necessary to resort to determination of the blood levels of cholesterol and other lipids, a very tangential approach. This has, however, already yielded some result. It would appear that the serum cholesterol levels in patients with overt coronary arteriosclerosis tend to be

significantly higher than in apparently normal subjects of the same age group, and also that the levels fluctuate much more widely. It has been known for some time, of course, that the diseases associated with marked and sustained hypercholesterolemia are frequently complicated by the precocious development of extensive arteriosclerosis.

Studies in man of the effects of diets high in cholesterol and fat indicate that they have surprisingly little influence upon serum cholesterol levels. This is not due to failure to absorb cholesterol since estimation of the fecal sterol content in such experiments has revealed that man has an unexpectedly large capacity to absorb dietary cholesterol in the form of egg-yolk powder. How much of the absorbed cholesterol is then metabolized and how much deposited in the tissues, a crucial point, has not, however, been possible of determination. It is uncertain, therefore, just what role the level of preformed cholesterol consumption may play in the production of arteriosclerosis.

The effects of low cholesterol, low fat diets have not yet been adequately studied. There are indications that the serum cholesterol levels may decline somewhat, at least temporarily; the effects on intimal lipid deposits are not known. Since acetate precursor for synthesis is readily available in dietary fat, protein and carbohydrate, restriction of preformed cholesterol in the diet may well have a limited although perhaps limiting effect.

At the present time attempts to prevent or minimize the development of arteriosclerosis in man would seem to be largely dependent upon the progress of animal experiments. These have arrived at the stage where it is possible to standardize the conditions necessary to induce arteriosclerosis regularly so that possible prophylactic or therapeutic agents, for example lipotropic agents, can be tested under reasonably controlled conditions. Such systematic programs are now being organized.

Clinico-pathologic Conference

Hepatosplenomegaly, Jaundice, Anemia and Recurrent Fever^{*}

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, J. H. Y., (B. H. No. 161904), a fifty-two year old white, married farmer, entered the Barnes Hospital on July 30, 1948, complaining of fever, weakness and weight loss. The patient was somewhat obtunded at the time of admission but fragmentary information was secured from him and from his daughter. The family history was apparently irrelevant. In regard to the past history it was stated that the patient had had typhoid fever many years before admission and that he occasionally had mild respiratory infections; otherwise, he apparently enjoyed excellent health and for many years had done hard physical labor while working his farm. He suffered a traumatic injury to his left eye many years ago.

Two years before admission to the Barnes Hospital the patient began having episodes of weakness. He consulted his physician several times and was told that he had "low blood pressure." One year before entry he noted numbness of both his lower extremities and his gait became unsteady; he complained that unless he could see them he was unaware of the position of his feet. Eight months before coming to the hospital he developed a febrile episode which lasted one week and which was diagnosed by his physician as "flu." Two months later chills and fever associated with nausea and vomiting appeared and persisted for two to three weeks. Diagnosis of malaria was made and quinine was pre-

scribed; the patient continued taking the drug daily until his entry to the Barnes Hospital. Subsequently the patient enjoyed a period of ten to fourteen days during which he was practically symptom-free. Attacks of chills and fever returned, however, and recurred repeatedly, each one lasting two to three weeks with periods of remission lasting one to two weeks; jaundice was thought to have been associated with some of the bouts. During the course of his illness penicillin was given on several occasions and six weeks before his entry to the Barnes Hospital he was taken to an outside hospital where he was said to have had "paralysis of the left arm and absent pain sensations in both legs." Severe anemia was discovered but only one blood transfusion was given since there was apparently considerable difficulty in finding suitable donors. After he left the hospital the patient was somewhat improved but for two months before entry he noted that his stools were black. One month before admission he developed pain in the right upper quadrant which recurred on several occasions and two weeks prior to entry there was slight epistaxis. About a week before his admission to the Barnes Hospital the patient developed high fever associated with almost continuous vomiting. During the course of his illness he had lost approximately 50 pounds.

Physical examination at the time of entry revealed the patient's temperature to be

^{*} From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

40.5°C., pulse 100, respirations 24 and blood pressure 90/60. The patient was a well developed but extremely emaciated male who appeared acutely ill. His skin was dry, pale, loose and hot, and signs of dehydration were pronounced. There was no significant lymphadenopathy. The conjunctivae were pale. The pupils reacted well to light and accommodation. There was an opacity of the lens of the left eye. Examination of the right optic fundus showed the vessels to be essentially normal, but one small, fresh hemorrhage was noted. The tongue was red and dry. The teeth were badly decayed. There was no distention of the neck veins and the trachea was in the midline. Examination of the lungs revealed them to be clear to percussion and auscultation. The heart was normal in size and contour and the rhythm was regular. The sounds were rather distant and there was a grade II systolic murmur. The liver edge was felt 8 cm. below the costal margin and was smooth and firm. The spleen extended 12 cm. below the left costal border and its edge likewise was firm. Rectal examination was negative. Neurologic examination revealed complete absence of all tendon reflexes but the sensory examination was unsatisfactory.

The laboratory data were as follows: Blood count: red cells, 1,900,000; hemoglobin, 4.5 Gm. per cent; white cells, 3,800; differential count: stab forms, 6 per cent; segmented forms, 54 per cent; lymphocytes, 36 per cent; monocytes, 4 per cent. Urinalysis: specific gravity, 1.010; albumin, 1+; sugar, negative; sediment, occasional red blood cell. Stool: guaiac negative. Blood Kahn test: negative. Blood chemistry: sugar, 106 mg. per cent; non-protein nitrogen, 50 mg. per cent; total protein, 6.8 Gm. per cent; albumin, 2.8 Gm. per cent; globulin, 4.0 Gm. per cent; chlorides, 90 mEq./L.; carbon dioxide combining power, 25 mEq./L.; cephalin-cholesterol flocculation test, 4+; icterus index, 10 units; thymol turbidity greater than 24 units. Electrocardiogram: low T waves in leads I and II.

Immediately upon admission to the

hospital the patient was given parenteral fluids and penicillin therapy was instituted. He likewise received large doses of vitamin B complex and vitamin C parenterally. Hematologic consultation was requested and the red count, white count and differential were found to be essentially those recorded during the routine admission studies. The platelet count was 585,000, the reticulocytes, 1.8 per cent. The cell indices were as follows: mean corpuscular volume, 80 cu. micra; mean corpuscular hemoglobin, 27 gamma gamma; mean corpuscular hemoglobin concentration, 34 per cent. Sternal marrow aspiration was performed and revealed a normal number of granulocytes with toxic granulation, marked decrease in the erythroid elements and a definite increase in the number of plasma cells and reticulum cells. There were many small, round cells, the identity of which was not clear.

Further laboratory studies performed at this time were as follows: Agglutinations against tularensis, brucella and typhoid antigens were negative; the circulation time (decholin) and venous pressure were within normal limits. Examination of the urine revealed that it contained bile but no Bence-Jones protein. The blood calcium was 9.4 mg. per cent; the phosphorus 5.2 mg. per cent; alkaline phosphatase, 9 Bodansky units; acid phosphatase, 3.9 King-Armstrong units and the chlorides, 103 mEq./L.

On the third hospital day the patient was typed and found to belong to group A, Rh positive. He was given two whole blood transfusions without immediate reaction, but on the following day jaundice was noted and the icterus index rose to 52.5 units. At that time the van den Bergh test was as follows: sodium bilirubinate, 6.3 mg. per cent; bilirubinglobin, 3.5 mg. per cent. Skin tests were performed with first and second strengths of purified protein derivative and with histoplasmin and coccidioidin; all were negative. Because the patient's temperature continued to be very high despite adequate penicillin dosage, he was started on streptomycin therapy on the

fifth hospital day, receiving a total dose of 1.2 Gm. daily. Desoxycorticosterone acetate was given in an attempt to correct persistent hypotension.

In the first three to four days of his hospital stay the patient continued to be somewhat obtunded but subsequently his sensorium cleared. On the sixth day a lumbar puncture was performed; the dynamics were normal as were the cell count, protein, colloidal gold curve and Wassermann. The temperature continued to range around 39°C. although occasionally it fell temporarily to lower levels. On the day before death repeat blood studies revealed the red count to be 2,070,000, hemoglobin, 5 Gm. per cent and white count, 3,400; the non-protein nitrogen had fallen to 32 mg. per cent, the carbon dioxide combining power was 27 mEq./L. and the chlorides were 101 mEq./L. The icterus index was 25 units and the total bilirubin was 3.2 mg. per cent. Repeated blood cultures were negative. On the final hospital day, August 7, 1948, the patient complained of being chilly; that night his temperature was 39.1°C. but he had no unusual complaints. Late that evening he called for a bed pan and when the nurse saw him a few minutes later he was dead.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Before we undertake discussion of this case I shall ask Dr. Grunow to comment on the x-ray films.

DR. OTTO H. W. GRUNOW: The chest film was not remarkable. The trachea was in the midline, the great vessels showed normal width and contour and the heart was not enlarged. There was no hilar adenopathy and both lung fields were entirely clear. An open film of the abdomen showed a small area of density in the right upper quadrant which conceivably represented a gallstone. Although the liver edge was described as extending 8 cm. below the costal margin, it did not appear abnormally large in the film. The kidney shadows were not outlined too well but the left kidney appeared to be displaced downward. The splenic flexure of the colon was likewise

depressed by a large mass in the left upper quadrant, presumably the spleen, but which conceivably might lie in the tail of the pancreas. Films of the lumbar spine were within normal limits.

DR. ALEXANDER: This case presents a difficult diagnostic problem, characterized by fever of unknown origin associated with anemia and hepatosplenomegaly in an acutely ill patient. This patient was also said to have had a systolic murmur and I should like to begin by asking Dr. Smith whether he thinks that a diagnosis of subacute bacterial endocarditis should be entertained.

DR. JOHN R. SMITH: Whenever a cardiac murmur is audible in a patient who has fever, splenomegaly and the other signs which were seen here, one must certainly consider that diagnosis. In this particular case, however, I do not believe that the diagnosis is very probable.

DR. ALEXANDER: The fact that this patient had a murmur, fever, a retinal hemorrhage and occasional red cells in the urine all suggest to me the diagnosis of bacterial endocarditis possibly due to one of the less common organisms. In the last few years at these conferences we have seen atypical cases of endocarditis due to fungi such as *Histoplasma capsulatum* or *Actinomyces*.

DR. THOMAS H. HUNTER: It would be most extraordinary for subacute bacterial endocarditis to continue for two years without any cardiac enlargement, pulmonary congestion or signs of cardiac failure.

DR. ALEXANDER: Dr. Massie, what is your view on this point?

DR. EDWARD MASSIE: I would agree with Dr. Hunter.

DR. W. BARRY WOOD, JR.: Is not leukopenia rather uncommon in subacute bacterial endocarditis?

DR. MASSIE: Yes, it certainly is but I have seen an occasional case in which leukopenia was present.

DR. ALEXANDER: Let us now consider the signs of liver disease. This man certainly had disturbed liver function. Dr. Duden,

would you comment on the possibility that the liver was primarily involved in the disease process?

DR. CHARLES W. DUDEN: Certainly hepatomegaly, splenomegaly, abnormal bleeding and signs of disturbed liver function lead one to consider diseases of the liver such as hepatitis or even cirrhosis, but I doubt that either of these represented the primary diagnosis.

DR. ALEXANDER: The patient had intermittent jaundice and the flat film of the abdomen showed a shadow which could have been a gallstone. Likewise, he had pain in the right upper quadrant. Dr. Scheff, could this man have had biliary obstruction with infection?

DR. HAROLD SCHEFF: I do not believe that the clinical picture observed here could possibly have been secondary to biliary obstruction. I should like to suggest Hodgkin's disease as a possibility.

DR. ALEXANDER: That is a very good suggestion but before we take it up I should like Dr. Moore to comment on the liver function tests and on the recurrent jaundice.

DR. CARL V. MOORE: Since there was an increase in both the sodium bilirubinate and sodium bilirubinglobin, I would be inclined to believe that this patient had intermittent biliary obstruction and hepatogenous jaundice.

DR. ALEXANDER: In addition to subacute bacterial endocarditis are there any other infectious diseases which should be considered?

DR. CARL G. HARFORD: Actually I do not believe this patient had an infectious disease but on the basis of the data at hand histoplasmosis should be considered.

DR. ALEXANDER: Your point is well taken in view of the clinical picture. If this patient indeed had had histoplasmosis, Dr. Moore, when the bone marrow studies were done, would it not have been likely that the organism would have been found?

DR. MOORE: With the exception of one case at the Children's Hospital, we have never found histoplasma by bone marrow aspiration. I have, however, seen cases in other clinics in which the diagnosis was

substantiated by that procedure. I am confident that had this man had histoplasmosis the organism would have been recovered from his bone marrow in view of the marked involvement of that tissue. I think we can say that this man had a granulomatous disease but I am not able to define the specific one at this time.

DR. ALEXANDER: Why do you believe that a granulomatous process is a most probable diagnosis?

DR. MOORE: The presence of persistent high fever, leukopenia without shift to the left in the presence of abnormal cells in the bone marrow, hepatomegaly, splenomegaly and involvement of the gastrointestinal tract all point to such a disease.

DR. ALEXANDER: I think you make a strong case for one of the so-called granulomas. Let us consider a few other diagnoses if only to eliminate them. Is undulant fever a very likely possibility, Dr. Harford?

DR. HARFORD: This patient's course would have been quite unusual for undulant fever since it was severe and progressive. Almost all of the signs are much more severe than would usually be expected in brucellosis.

DR. ALEXANDER: Would one not have expected the blood cultures to have been positive had this patient had brucellosis?

DR. HARFORD: Yes, the likelihood of the organism having been recovered upon repeated blood cultures would have been good although, of course, negative blood cultures do not completely rule out the disease.

DR. ALEXANDER: What about the agglutination test?

DR. HARFORD: The negative agglutination test also constituted evidence against the diagnosis of brucellosis, particularly at this advanced stage.

DR. MOORE: I should like to ask Dr. Harford about the results of the skin tests for tuberculosis, histoplasmosis and coccidioidomycosis. Should doubt be cast on the negative skin tests in view of the extreme severity of this man's illness?

DR. HARFORD: It is probably true that skin tests are less reliable in a terminal illness; especially in tuberculosis a so-called anergic state is said to occur in the agonal stage of the disease.

DR. MARGARET G. SMITH: At the Children's Hospital recently a child who at autopsy was found to have histoplasmosis had repeatedly negative skin tests with histoplasmin.

DR. ALONZA L. FARR: There are recent reports in the literature of patients with proven histoplasmosis who had positive skin tests. In these patients, however, the skin tests were usually performed repeatedly and it is conceivable that the positivity was due to development of hypersensitivity not as a result of the disease *per se* but rather because of repeated exposure to the test antigen. There is also a report of nine patients with fatal histoplasmosis in five of whom histoplasmin skin tests were negative. Since a very large percentage of the population in this part of the country have positive histoplasmin skin tests, I do not see that too much stress can be placed on the results one way or the other.

DR. MASSIE: I should like to ask Dr. Moore to comment on the neurologic findings in regard to the anemia.

DR. MOORE: Nothing in the hematologic findings suggested the diagnosis of pernicious anemia. I believe that the neurologic findings were more likely due to multiple vitamin deficiency which the patient probably had for a long time and which may have been exaggerated by the persistent high fever. I am unable to explain the neurologic manifestations in terms of the blood findings.

DR. ALEXANDER: It was stated that when the patient was admitted to the outside hospital his arm was paralyzed. No evidence of such paresis was observed on his examination here.

DR. HARFORD: Is it conceivable that the fact that this patient took quinine for a long period of time may have given rise to a state of hypersensitivity which may have been responsible for the terminal illness?

DR. ALEXANDER: I have never seen hypersensitivity to quinine in my experience. Perhaps, Dr. Saunders would discuss this point.

DR. GEORGE M. SAUNDERS: We saw many natives in endemic malarial regions who had taken quinine for long periods of time without ever developing sensitivity.

DR. ALEXANDER: Let us now attempt to define further what granulomatous disease this patient may have had. Dr. Moore, you said that the bone marrow aspiration showed some unusual small cells. Are you now able to dilate further on their nature?

DR. MOORE: No, I cannot. They were either lymphocytes or so-called primitive cells. There is a great deal of discussion among hematologists in regard to the nature of the latter; they are frequently seen but I do not believe that they have specific diagnostic significance. The increase in reticulum cells and plasma cells was compatible with any granuloma.

DR. ALEXANDER: In view of the increase in plasma cells and the high serum globulin should multiple myeloma be considered?

DR. MOORE: I believe multiple myeloma is extremely unlikely.

DR. ALEXANDER: Dr. Scheff, you suggested Hodgkin's disease. On what features do you base your suggestion?

DR. SCHEFF: Anemia, hepatosplenomegaly and gastrointestinal symptoms may all be identified with Hodgkin's disease. Furthermore, the remittent fever brings to mind so-called Pel-Ebstein fever which is said to be particularly common in abdominal Hodgkin's disease.

DR. ALEXANDER: Is intermittent jaundice compatible with your interpretation?

DR. SCHEFF: It is not common but may occur if the liver is involved.

DR. ALFRED GOLDMAN: Is not jaundice in Hodgkin's disease more often due to so-called acute acquired hemolytic anemia?

DR. MOORE: Yes, that is correct. Hemolytic jaundice may occur in Hodgkin's disease. Occasionally, intermittent biliary obstruction is seen when enlarged lymph nodes impinge on the common bile duct.

It would be quite difficult to explain hepatogenous jaundice in Hodgkin's disease and I am not sure that I can suggest a suitable mechanism for it. It should also be remembered that this patient had an increase in jaundice after transfusion; that conceivably could have been due to homologous serum jaundice or perhaps the cells were hemolyzed following transfusion although they were compatible as far as cross matching was concerned.

DR. ALEXANDER: Is leukopenia of any aid in differential diagnosis?

DR. MOORE: No, it may occur in any granulomatous disease.

DR. WOOD: Dr. Moore mentioned granulomatous diseases and so far we have discussed histoplasmosis, brucellosis and Hodgkin's disease. What other granulomatous diseases was he considering?

DR. MOORE: The term may be used to include tularemia, paratyphoid fever or tuberculosis. I do not think that tuberculosis is a very good possibility.

DR. ALEXANDER: Dr. Fields, would you comment on the neurologic findings?

DR. WILLIAM S. FIELDS: If it had been possible to do a satisfactory sensory examination at the time that the patient was admitted to the hospital, we would perhaps be in a better position to discuss this point. His neurologic complaints began two years before admission, and at one time he was said to have had paralysis of one arm. The earlier findings suggest involvement of the dorsal lateral portion of the cord, but the improvement is hard to explain.

DR. DUDEN: Although there is much against a diagnosis of pancreatic malignancy, some of the findings would be in keeping with that possibility. Carcinoma of the body or tail of the pancreas is often identified with idiopathic venous thromboses, and it is conceivable that portal vein thrombosis could have given rise to the large liver and spleen and that venous thromboses in the cord might have explained the neurologic findings.

DR. ALEXANDER: I think that is a very interesting suggestion.

A STUDENT: Does the presence of toxic granulation rule out malignancy?

DR. MOORE: Since many forms of malignancy may give rise to persistent fever and since fever is often identified with toxic granulation of the polymorphonuclear leukocytes, I do not think that the finding is of any value in differential diagnosis.

DR. ALEXANDER: Dr. Goldman, Dr. Moore dismissed tuberculosis as an unlikely possibility. What is your belief on this point?

DR. GOLDMAN: In this particular case tuberculosis in the absence of any pulmonary involvement would be most unusual. We have seen it limited to the spleen and liver and when it does involve the liver abnormalities in the peripheral blood frequently occur. I think the negative purified protein derivative skin tests mitigate against the diagnosis of tuberculosis despite the fact that in terminal cases anergy occasionally does occur.

DR. SAMUEL B. GUZE: I have seen cases in which the Division of Hematology has made a diagnosis of reticulum cell sarcoma, presumably on the basis of bone marrow studies. In this case reticulum cells were described in the bone marrow smear. Would Dr. Moore comment on the factors involved in arriving at the diagnosis of reticulum cell sarcoma on the basis of bone marrow findings?

DR. MOORE: If we made a diagnosis of reticulum cell sarcoma on the basis of the bone marrow examination alone, we were probably over confident. The only time that such a diagnosis can be made on that basis is when the number of reticulum cells is very great and when there are easily demonstrable mitotic figures within the reticulum cells themselves.

DR. ALEXANDER: Dr. Moore, which of the so-called lymphoma group would you think was the most likely considering all of the evidence here?

DR. MOORE: I think the findings are more in keeping with Hodgkin's disease than they would be with any of the other forms of lymphomas such as reticulum cell sarcoma or lymphosarcoma.

DR. WOOD: On one occasion when this patient had a temperature of approximately 40°C. he was given 1.2 Gm. of aspirin and his temperature fell dramatically to within normal limits. Sometime ago we had another patient with Hodgkin's disease with a high temperature and following a similar dose of aspirin his temperature fell to 35°C. At the time we consulted the literature and found that patients with Hodgkin's disease who have fever may be very sensitive to the antipyretic action of salicylates. Perhaps our observation in this case adds further evidence in favor of the diagnosis of Hodgkin's disease.

DR. ALEXANDER: Do you favor Hodgkin's disease, Dr. Wood?

DR. WOOD: Yes, I believe this man had a granulomatous disease, probably one of the lymphomas and among the lymphomas I would rate Hodgkin's disease the most likely.

DR. ALEXANDER: In summary then, this acutely ill patient with fever, hepatomegaly, splenomegaly and severe anemia is thought probably to have had Hodgkin's disease, but other granulomatous diseases, such as histoplasmosis, tuberculosis and brucellosis, have been considered and malignancy of the tail and body of the pancreas has also been mentioned. We shall ask the pathologists to clarify the situation for us.

Clinical Diagnosis: Hodgkin's disease.

PATHOLOGIC DISCUSSION

DR. ELI M. NADEL: At autopsy the axillary, cervical and inguinal lymph nodes were not enlarged. There were 500 cc. of fluid in the right pleural cavity and 350 cc. in the left.

The lungs weighed 1,900 Gm. There were a few fibrous adhesions on the lateral surface of the upper lobe of the right lung. Grey, confluent, fibrinous areas were present in both lungs together with a moderate amount of emphysema, congestion and edema. The tracheobronchial lymph nodes were moderately enlarged. Acute tracheobronchitis was present.

The pericardial sac contained 30 cc. of clear fluid. The heart weighed 350 Gm.; the cut surface of the myocardium was pale and the entire organ was moderately flabby. A few small, fibrous adhesions of the pericardium were noted in the atrioventricular groove.

The peritoneal cavity contained 250 cc. of clear fluid. A few fibrous adhesions were present between the omentum, gallbladder, liver, duodenum and colon. There was a calcified omental tag adherent to the gallbladder. The liver was markedly enlarged, weighing 2,780 Gm. The surface was smooth and the cut edge was pale, showing uniform enlargement and prominence of the individual lobules. The spleen was markedly enlarged; it weighed 1,370 Gm. The capsule over its lateral surface had a puckered, calcified area of thickening 3 cm. in diameter. The cut surface of the spleen was soft and bulged and there were many fairly well defined grey areas having an average diameter of 3 to 4 cm. The splenic pulp was congested.

Both kidneys were enlarged; the left weighed 240 Gm. and the right 210 Gm. Both capsules were moderately adherent. There was congestion in the cortex and medulla but the corticomedullary junction was well defined. There was generalized mottling of the surface by confluent grey areas. Over the surface of the upper pole white areas were seen. The pelves and ureters were grossly normal.

The adrenals were small, weighing together only 11 Gm. The cortices were thin and poor in lipids.

There was moderate enlargement of all of the retroperitoneal and peripancreatic nodes. Nodes along both curvatures of the stomach and in the protahepatic regions were similarly enlarged but the mesenteric nodes were not remarkable in size. The enlarged nodes were discrete, movable, elastic and on cut surface showed a predominance of grey uniform tissue.

Congestion, ecchymoses and petechiae were noted in the mucosa of the urinary bladder and gastrointestinal tract.

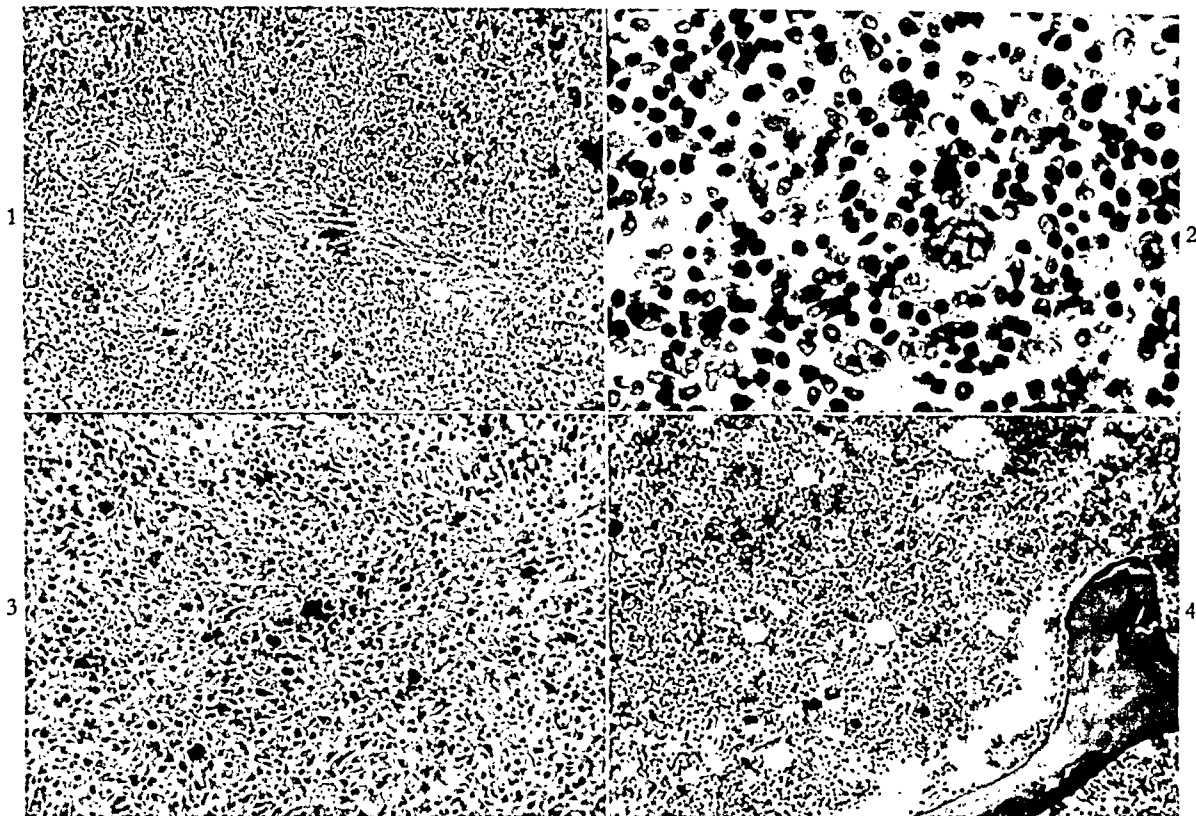


FIG. 1. Fibrosis and infiltration of Hodgkin's tissue with multinucleated giant cells in the spleen.

FIG. 2. Multinucleated giant cells, with prominent nucleoli and chromatin of the typical Reed-Sternberg type, and plasma cells in a section of spleen. Similar cells were present in lymph nodes, bone marrow, lungs, liver and kidneys.

FIG. 3. Focus of involvement of the bone marrow by Hodgkin's disease.

FIG. 4. Sections of hyperplastic bone marrow from portions not directly involved by Hodgkin's disease.

DR. MARGARET G. SMITH: On the basis of the gross findings we were not ready to make a definitive diagnosis. So large a spleen with such minimal involvement of the abdominal lymph nodes is certainly unusual in Hodgkin's disease. Figure 1 is a moderately low power photomicrograph of the spleen; it shows an increase of fibrous tissue around the small arterioles and loss of the normal architecture of the spleen. A considerable number of very large cells may be seen. In Figure 2 these large cells are shown under higher power; they are characterized by multiple nuclei, prominent nucleoli and definite nuclear membranes. Other similar cells having a single nucleus are also present as are a considerable number of plasma cells and lymphocytes; there is only an occasional eosinophilic leukocyte. The number of plasma cells in the spleen and other organs was somewhat greater than

one usually finds in Hodgkin's disease but cases have been described in which plasma cell infiltration was conspicuous. We made a diagnosis of Hodgkin's disease on the basis of the microscopic appearance of these two sections.

The next section (Figure 3) is from the bone marrow and the findings again are quite consistent with the diagnosis of Hodgkin's disease. There is an increase in collagen and in the large cells with vesicular nuclei and prominent nucleoli; again a considerable number of lymphocytes and plasma cells which are not seen well in this photograph were identified. Areas such as this one were quite widespread through sections of vertebral marrow. The next section (Fig. 4) is of uninvolved marrow and shows hyperplasia of the erythroid and myeloid elements. Even in such areas as this in which there was relatively normal blood formation

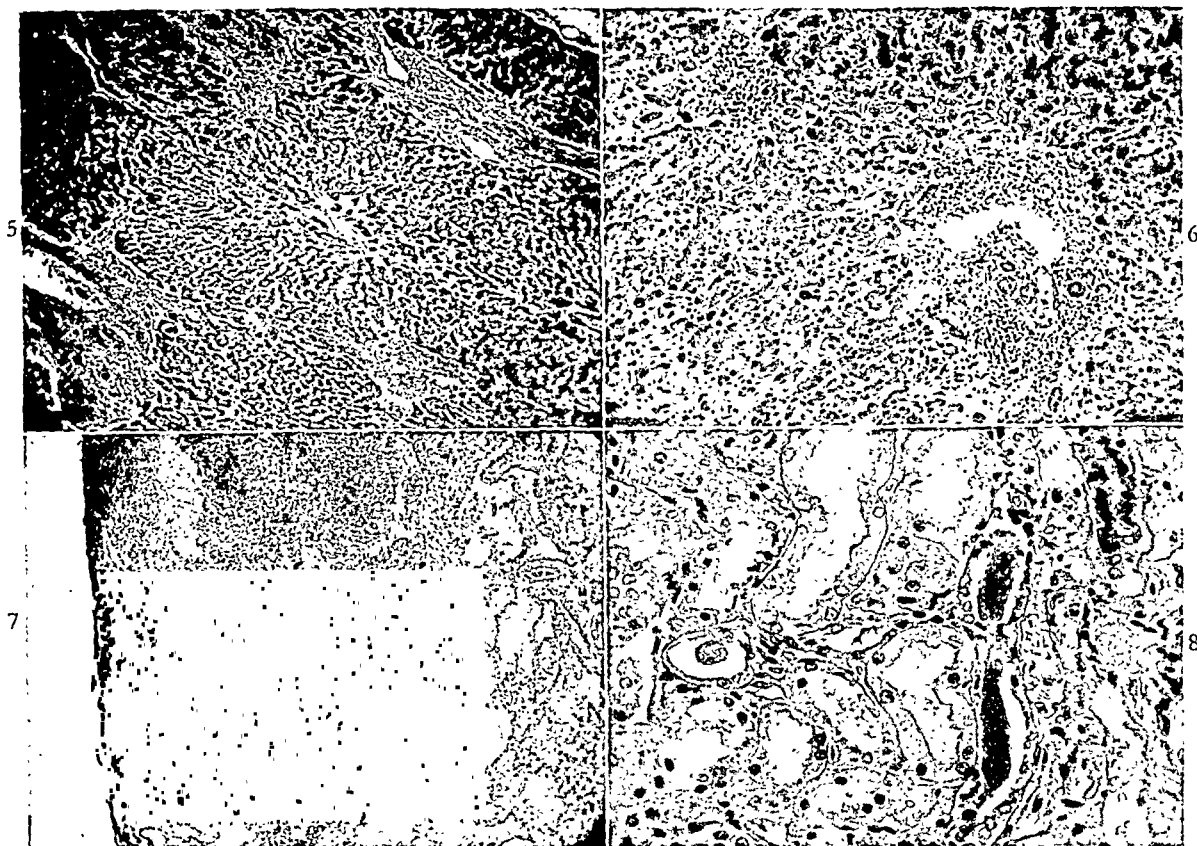


FIG. 5. Portal areas of the liver infiltrated by Hodgkin's disease and containing slight proliferation of small bile ducts.

FIG. 6. Infiltration and increased fibrous tissue in the portal spaces and central atrophy of the hepatic cords.

FIG. 7. Focus of involvement of the lung by Hodgkin's disease with congestion and edema of the uninvolved alveoli.

FIG. 8. Hemoglobin cast in one renal tubule and granules of iron in the epithelium of a tubule in the right upper corner.

plasma cells were present. Sections from some of the lymph nodes exhibited changes diagnostic of Hodgkin's disease but at least one node from the abdominal cavity showed practically no such change. In general there was minimal involvement of the lymph nodes but plasma cells were prominent.

In the periportal tissue throughout the liver there is infiltration of cells of types similar to those seen in other organs. (Fig. 5.) There is also marked atrophy of the hepatic cords in the central portions of the lobules, possibly associated with the severe anemia. Some fibrosis is present in the tissues about the portal zones and a little proliferation of the bile ducts in those areas is noted, again with the characteristic giant cells present. Figure 6 presents a higher power view of these findings.

In Figure 7 a small area of Hodgkin's

tissue in the lung is shown. There is fibrosis in what appears to be a nodule of lymphoid tissue; plasma cells and the characteristic large cells of Hodgkin's disease are present. The marked edema in the alveoli represents a terminal phenomenon.

The kidneys were quite large and had a mottled appearance. Figure 8 shows a tubule deep in the cortex near the edge of the medulla. It contains a cast which had the brick red color characteristic of hemoglobin pigment. There is also destruction of the epithelium of this particular tubule. In the cells of an adjacent tubule very definite brown granules are present, probably iron. There is also swelling of the epithelium in the convoluted tubules and edema of the interstitial tissue. We thought that these findings were compatible with the changes of hemoglobinuric nephrosis

although of a very slight degree. A small nodule showing the characteristic changes of Hodgkin's disease was also present in the kidney.

This case had some unusual features. The microscopic observations were quite characteristic of Hodgkin's disease although the large number of plasma cells was somewhat unusual. Another uncommon feature was the limited and inconstant involvement of lymph nodes. There are several cases in the literature, however, in which only slight involvement of the lymph nodes was present. One such example was reported by Dr. Krumbhaar;¹ he cited a case in which although the spleen was very large there was no involvement of the lymph nodes. Another case was reviewed by Steiner in which there

was involvement of the bones and liver with no involvement of the lymph nodes.¹

Thus, despite the atypical gross aspects, the microscopic findings in this case were characteristic of Hodgkin's disease and a definitive diagnosis could be established.

Pathologic Diagnoses: Hodgkin's disease involving the spleen, bone marrow, liver, abdominal lymph nodes, lung and kidney; congestion and edema of the lungs; hydrothorax (right 300, left 350 cc.); hydroperitoneum (250 cc.); ecchymoses and petechiae in the gastrointestinal tract, urinary bladder and adventitia of the ascending aorta; hemoglobinuric nephrosis, slight.

Editor's Note: Reprints of these conferences are now available. Requests should be sent to Dr. Robert J. Glaser, Department of Medicine, Barnes Hospital, St. Louis 10, Mo.

¹STEINER, P. E. Hodgkin's disease. *Arch. Path.*, 36: 627, 1943.

¹KRUMBHAAR, E. B. Hodgkin's disease of bone marrow and spleen without apparent involvement of lymph nodes. *Am. J. M. Sc.*, 182: 766, 1930.

Spontaneous Hemopneumothorax with Recovery*

VIRGIL J. DORSET, M.D. and LUTHER L. TERRY, M.D.

Baltimore, Maryland

ALTHOUGH spontaneous pneumothorax is a common condition, the sudden occurrence of blood and air in the pleural cavity of an apparently healthy individual is rare. In 1942 Hartzell⁴ collected forty published cases with references and presented an excellent review of the literature on the subject. At the same time he reported four additional cases observed at the Cleveland City Hospital during a ten-year period. Further search of the literature prior to 1942 revealed four other cases not mentioned by Hartzell which were reported by Bouchut and Beaupere in 1924,¹ Doris in 1928,² Leggett, Myers and Levine in 1934⁷ and Maxwell in 1938.⁸ Since 1942, six additional cases have been reported by Tannenbaum,¹¹ Snively, Shuman and Snively,¹⁰ Lea,⁶ Payn and Lief,⁹ Franklin³ and Helwig and Schmidt.⁵ The report of Helwig and Schmidt presented a review of the thirteen fatal cases upon which autopsy studies were available and added one case of their own.

Thus, medical literature contains reports of approximately fifty-four cases of spontaneous hemopneumothorax and autopsy findings on fourteen of those who died.

The following report is that of hemopneumothorax occurring in a healthy young individual who was carefully studied at the time and who has remained well for one year following the attack.

CASE REPORT

M. W. L., a twenty-seven year old white female employed as a surgical ward secretary in this hospital, was admitted August 4, 1946, complaining of pain in her left chest.

She stated that during the night of August 2, 1946, she noticed pain between her scapulae. The following day she had slight pain in her left chest, exaggerated at times by deep inspiration. A slight non-productive cough developed. When bending over, she noticed a "rolling sensation" in her left chest. On the evening of August 3rd she took a hot bath, felt better and went to a baseball game. Later that evening at home she experienced severe left chest pain which extended from the sternum to the vertebral column. The following day continued pain in the left chest and shoulder and a non-productive cough caused her to seek medical attention.

Past history revealed that the patient had had a similar attack of pain in her left chest in April, 1946 which lasted for eight hours. X-ray of the chest at that time showed no evidence of disease. She denied any past history suggestive of tuberculosis and denied any contact with tuberculous persons.

Physical examination disclosed a fairly well developed and well nourished white female twenty-seven years of age who was propped up in bed on pillows. Blood pressure was 134/94, temperature 37.2°C., pulse 120 and respirations 20. She appeared pale but not acutely ill and was not dyspneic at rest. Examination of the head and neck revealed no pertinent findings. Some lag of the left chest was noted on deep inspiration. There was dullness on percussion, absent vocal fremitus and distant to absent breath sounds over the lower left chest, especially posteriorly. No rales were heard. Heart size, sounds and rhythm were normal. The abdomen was soft and pliable. Some tenderness to pressure was noted at the left costovertebral angle. The liver and spleen were not palpable. The extremities were normal.

Laboratory data: Urinalysis was normal. Kline and Kahn serologic tests were negative. The platelet count was 340,000, bleeding time

* From the Medical Service of the U. S. Marine Hospital, U. S. Public Health Service, Baltimore, Md.



FIG. 1. X-ray of chest on admission showing hemopneumothorax on left.

2 minutes, coagulation time by the tube method 9 minutes and prothrombin time 13 seconds, control 11 seconds.

X-ray of the chest on admission showed a left hydropneumothorax with the fluid level at the second interspace anteriorly. (Fig. 1.) The entire right lung was clear and the heart shadow was not significantly displaced. An electrocardiogram was within normal limits.

Shortly after admission a diagnostic thoracentesis was performed and revealed fluid which had the appearance of whole blood. Only 120 cc. was removed but the patient noted a considerable decrease in the left chest discomfort. Further aspirations were performed every few days and it was noted that the fluid gradually became less bloody. The date and quantities of fluid removed as compared with peripheral blood findings are shown in Table 1. There was no evidence of further bleeding after admission. Her temperature occasionally reached 37.6°C. (99.7°F.) during the first week of hospitalization but remained normal thereafter. Penicillin was given parenterally for the first nine days and 50,000 units were instilled in the chest at the time of each aspiration. Ferrous sulfate, multivitamins, ascorbic acid and vitamin K were given by mouth. There was a gradual rise in the hemoglobin and red cell count of the peripheral blood. The patient improved symptomatically as the amount of chest fluid decreased. She was discharged on the twenty-seventh hospital day, at which time x-ray revealed almost complete re-expansion of the lung with a small amount of fluid remaining in the left costophrenic sulcus.

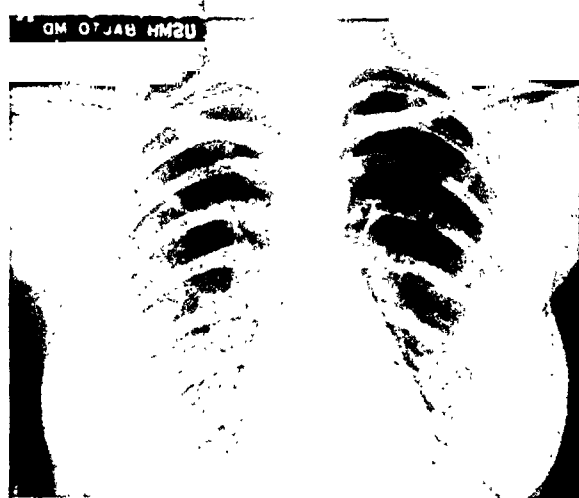


FIG. 2. X-ray of chest fourteen months after hemopneumothorax showing completely normal appearance throughout.

On September 17, 1946, x-ray examination of the chest showed the lung fully expanded but a small amount of fluid still remained in the costophrenic sulcus. The patient was asymptomatic except for occasional mild discomfort in the left chest; the blood count was essentially normal. She was allowed to return to duty on October 7, 1946.

During the twelve months subsequent to the attack the patient was seen at frequent intervals and x-rays of the chest were obtained about every two months. A film on November 6, 1946, showed complete absorption of all fluid and x-rays showed both lungs to be completely clear on all occasions. An x-ray of the chest obtained on September 30, 1947, fourteen months after the initial attack, revealed normal lung fields. (Fig. 2.) Subsequent x-ray examinations, the last of which was taken on May 19, 1948, approximately twenty-one months after the onset, also were clinically negative. The patient has resumed her normal life and has remained well. She complained of occasional mild discomfort in the left chest but otherwise was completely asymptomatic.

Guinea pig inoculation with the chest fluid failed to show any evidence of tuberculosis. Skin test with the first test dose of purified protein derivative (0.00002 mg.) showed a positive reaction in forty-eight hours.

COMMENTS

Review of the literature on spontaneous hemopneumothorax reveals that all of the

previous cases but one have occurred in males. This is the second reported case in a female. The average age of all patients has been twenty-six years, with a range from seventeen to forty-four years of age.

The etiology of spontaneous hemopneu-

terminated and in three cases no lesions of the collapsed lung could be found.

The onset of symptoms in most reported cases was characterized by pain in the involved side of the chest followed in a few hours, or days in some instances, by weak-

TABLE I

Date	Peripheral Blood				Aspirated Chest Fluid					
	Red Blood Cells	Hemo-globin	White Blood Cells	Sedimen-tation Rate (mm. hr.) (Win-trobe)	Red Blood Cells	Hemo-globin	White Blood Cells	Specific Gravity	Culture	Fluid Aspirated (cc.)
8-5-46	3,000,000	8.5	13,400	..	2,700,000	8	6,500	1.040	no growth	120
8-7-46	250
8-12-46	3,000,000	10.0	11,600	250
8-15-46	3,000,000	11.5	300
8-20-46	21	400
8-23-46	502
8-26-46	3,900,000	12.5	7,500	11	3,100	..	8,700	1.024	no growth	235
9-17-46	4,200,000	13	Total aspirated					2,057 cc.
11-6-46	13	10,000	9						
8-4-47	4,640,000	12.5	12,500	14						

mothorax is not clear but most authors believe that it is not different from spontaneous pneumothorax. They believe that the bleeding is simply a complication of the latter condition and that it is due to rupture of an emphysematous bleb or of a pleural adhesion. However, the majority of cases reported have not been associated with unusual physical or respiratory exertion. Other authors have attributed the condition to small unrecognized tuberculous lesions. Helwig and Schmidt,⁵ in a recent review of the autopsy findings on fourteen cases, showed that the source of the bleeding was not demonstrated in half of the cases. However, the majority of the patients showed apical pleural scars and six had adhesions involving the lung. Emphysematous bullae were observed ten times, ruptured bullae four times and torn pleural adhesions five times. In many instances the origin of the pneumothorax was not de-

ness, dyspnea, pallor and faintness. The interval between the onset of pain and the signs of shock was apparently dependent upon the rate of blood loss. In some cases the presenting symptom was abdominal pain. Exploratory laparotomy was considered not infrequently and two patients were operated upon with negative findings resulting. Nausea, vomiting, diarrhea and pain in various parts of the abdomen were mentioned in several cases.

The physical findings were usually those of pneumothorax with fluid. Mediastinal shift was noted as a rule in cases of massive hemorrhage and was usually associated with a weak thready pulse, low blood pressure, sweating and dyspnea. Low grade fever and moderate to severe secondary anemia were found as a rule. The leukocyte counts varied from 6,000 to 20,000. Sputum examinations were invariably negative for acid-fast bacilli. Platelet counts,

prothrombin, bleeding and coagulation times were normal when obtained.

The clinical course of most patients who survived the initial period of shock and who showed no signs of continued bleeding was that of gradual steady improvement and recovery without complications. However, fourteen of the fifty-four reported cases terminated fatally. No cases of recurrent spontaneous hemopneumothorax were found in the literature, in contrast to rather frequent instances of recurrent spontaneous pneumothorax.

The treatment of spontaneous hemopneumothorax was considered by most authors on this subject to depend upon the degree of hemorrhage and shock. It would appear that unless there is marked respiratory distress only a small amount of fluid should be removed initially for diagnostic purposes. In the event of continued bleeding transfusions of whole blood are indicated. Complete bed rest and sedation are important in the early stages. Signs of continued bleeding might possibly indicate the need for thoracoscopy and cauterization of the bleeding point. Once the first few critical days have passed aspiration of 200 to 500 cc. of blood should be done every few days, with partial replacement of the fluid by air. If the blood is not removed, calcification of the pleura and secondary cardiac complications may occur.

SUMMARY

1. A case of spontaneous hemopneumothorax in a twenty-seven year old woman who was apparently well prior to the attack is reported. Careful follow-up for fourteen months subsequently failed to reveal any evidence of pulmonary disease.

2. The literature on this relatively rare condition is discussed briefly, with relation to etiology, clinical course and treatment.

REFERENCES

1. BOUCHUT and BEAUPERE. Hemopneumothorax spontané chez un jeune sujet. *Lyon M.*, 138: 283-284, 1926.
2. DORIA, R. Emopneumotorace spontaneo con versamento bloccato. *Riforma med.*, 44: 552-554, 1928.
3. FRANKLIN, J. Spontaneous hemopneumothorax: report of a case occurring in a soldier. *Ann. Int. Med.*, 23: 437-441, 1945.
4. HARTZELL, H. C. Spontaneous hemopneumothorax. *Ann. Int. Med.*, 17: 496-510, 1942.
5. HELWIG, F. C. and SCHMIDT, E. C. H. Fatal spontaneous hemopneumothorax. *Ann. Int. Med.*, 26: 608-617, 1947.
6. LEA, R. G. Spontaneous hemopneumothorax. *Canad. M. A. J.*, 46: 371-373, 1942.
7. LEGGETT, E. A., MYERS, J. A. and LEVINE, I. Spontaneous pneumothorax. *Am. Rev. Tuberc.*, 29: 348-361, 1934.
8. MAXWELL, J. Spontaneous hemopneumothorax. *Brit. M. J.*, 1: 778, 1938.
9. PAYN, S. B. and LIEF, V. F. Spontaneous hemopneumothorax. *Bull. U. S. Army M. Dept.*, 3: 94-99, 1945.
10. SNIVELY, D., SHUMAN, H. and SNIVELY, W. D. Spontaneous hemopneumothorax. *Ann. Int. Med.*, 16: 349-356, 1942.
11. TANNENBAUM, M. Spontaneous hemopneumothorax. *Dis. of Chest*, 8: 178-181, 1942.

Editorial

Coronary Failure and Coronary Arteritis

EVERY doctor is thoroughly familiar with the clinical features of Heberden's angina pectoris as well as with those of acute coronary thrombosis with cardiac infarction. The peculiar paroxysmal precordial pain brought on by effort or emotion and relieved by rest or by nitroglycerin in the former, and the steady and prolonged distress often associated with shock, requiring morphine and not relieved by vasodilators in the latter, usually lead to easy and certain diagnosis. Less well understood, however, are those syndromes which seem to occupy an intermediate position between typical angina and cardiac infarction. A patient, usually with a known background of coronary disease, experiences bouts of precordial, substernal or arm pain often coming on at rest and not necessarily after exercise or after any obvious emotional aggravation. Such attacks may last for hours or days; they are not adequately relieved by nitrites and yet there is no definite evidence of cardiac infarction. In the type of case to which we allude there is no fever, leukocytosis, alteration in sedimentation rate or progressive electrocardiographic change in association with the bout of pain. Now this is clearly not typical Heberden's angina in the sense of a transitory anoxia or ischemia of the heart muscle, nor does it seem probable that episodes of such prolonged grumbling pain, repeated perhaps a number of times during a period of days or weeks, could correspond to an equal number of distinct coronary thromboses or cardiac infarctions.

In a recent paper Freidberg, Blumgart, Zoll and Schlesinger¹ discuss the problem of these syndromes more or less intermediate between angina pectoris and cardiac infarction. Autopsies are reported in a number of patients which show ample evidence of coronary disease—arteriosclerosis, old and fresh coronary thromboses, ulceration of atheromatous plaques—but no accurate correlation between the bouts of pain which the patient had experienced and the evidences of infarction was possible. The writers give it as their opinion that pain in these cases is essentially of the same nature as that occurring in the other coronary syndromes. They believe that the distress is due to a relative anoxia of heart muscle. This is presumed to lead to the accumulation of metabolic products which in turn act on pain nerve endings in the heart, especially in the vessels. The absence of evidence of infarction by clinical tests and perhaps at autopsy as well is explained by the presumption that the ischemia is not of sufficient degree to cause actual death of a portion of heart muscle. The term "coronary failure" is endorsed by Freidberg and his associates as an appropriate designation for these "intermediate" coronary syndromes.

It seems of interest, however, to consider a different explanation for the pain in some of these cases, namely, the possibility that it may arise directly from a lesion in the vessel wall. That an injury to the arterial

¹ FREIDBERG, A. S., BLUMGART, H. L., ZOLL, P. M. and SCHLESINGER, M. J. Coronary failure. *J. A. M. A.*, 138: 107, 1948.

wall gives pain one can readily convince himself of by having a puncture of his radial artery done without anesthesia and with a dull needle. An exquisite attack of anginal distress in reverse is produced; the pain radiates up the arm to the precordium. Pain arising directly from disease of arterial walls is also to be seen with a split in the aorta such as occurs in cases of dissecting aneurysm, with syphilitic aneurysm and perhaps in certain diseases of the peripheral arteries. Experimentally also the ingenious observations of Gorham and his associates² showed that pain can be produced by tri-directional traction on the wall of a coronary artery, without evident narrowing of the lumen and without electrocardiographic changes. Katz³ also pointed out that occlusion of carefully isolated strips of coronary artery in the dog yielded no evidence of pain nor did pain result from the crushing of arterial strips in which the nerves had been destroyed by phenol. In brief, then, one wonders whether in some of these patients with prolonged "coronary" pain not anginal in type and without evidence of cardiac infarct the distress may not, in part at least, arise directly from a lesion in the vessel wall rather than wholly as the result of myocardial ischemia. One may suggest the possibility that in a person who has coronary disease, hemorrhage into the vessel wall or some progression or alteration in an atherosclerotic patch could directly cause the artery to become painful, that such pain could come and go over variable periods of time, that nitrites would not be expected to relieve whereas morphine would,

and that evidences of infarction and striking electrocardiographic changes would not be anticipated. Furthermore, the sequence of events often seen, of precordial aching later followed by full evidence of thrombosis and infarct may be explained by the fact that a painful lesion in the vessel wall finally comes to the internal surface with formation of intra-arterial clot. Blumenthal and Reisinger⁴ have suggested that intramural hemorrhage under these conditions may provoke pain by tension on the adventitia. Still further evidence that pain may arise in arteries is presented by Wolff⁵ in his monograph on headache.

If it should turn out that certain types of coronary pain arise directly from a lesion in the vessel wall, *coronary arteritis* would seem to be a simple designation even if not an entirely accurate one. Perhaps a better term could be found. No doubt both "coronary arteritis" and coronary failure could contribute to the clinical phenomena in various cases, and further work would be necessary to evaluate the relative importance of these components in the individual. The matter is not one of academic interest alone but has a very practical side in the planning of treatment. If pain is caused early by a lesion still confined to the interior of the vessel wall, dicumarol might be invaluable in preventing coronary thrombosis from occurring later, and indeed might be of greater use than after frank occlusion and infarction have supervened. If on the other hand pain is due merely to disproportion between the coronary lumen and the need for blood on the part of the myocardium, there would be less immediate indication for anticoagulant therapy.

ARTHUR L. BLOOMFIELD, M.D.

² MARTIN S. J. and GORHAM, L. W. Cardiac pain: An experimental study with reference to the tension factor. *Arch. Int. Med.*, 62: 840, 1938.

³ KATZ, L. N., MAYNE, W. and WEINSTEIN, B. S. Cardiac pain: presence of pain fibers in the nerve plexus surrounding the coronary vessels. *Arch. Int. Med.*, 55: 760, 1935.

⁴ BLUMENTHAL, B. and REISINGER, J. A. Prodromal pain in coronary occlusion. *Am. Heart J.*, 20: 141, 1940.

⁵ WOLFF, HAROLD, G. Headache and Other Pain. New York, 1948. Oxford University Press.

Multiple Myeloma*

Its Clinical and Laboratory Diagnosis with Emphasis on Electrophoretic Abnormalities

W. S. ADAMS, M.D., E. L. ALLING, M.D. and J. S. LAWRENCE, M.D.†

Rochester, New York

THIS report deals with the clinical and laboratory findings in sixty-one cases of multiple myeloma. Particular emphasis has been placed on the importance of the occurrence of electrophoretic abnormalities in this disease. It is hoped that a report of these findings will be useful to others in making an early and accurate diagnosis of multiple myeloma.

HISTORY

In 1845 a forty-seven year old grocer who had been "out of health for thirteen months" was seen by his physician, Sir James Watson. A peculiar substance which solidified on cooling was noted in the urine. Being curious as to the nature of this substance both Dr. Watson and Dr. MacIntyre, the latter having been called in consultation, sent samples of the urine to Henry Bence Jones.¹ After considerable study Bence Jones found that this unusual urinary substance precipitated on heating, cleared on boiling and returned to a solid state on cooling. He also noted at necropsy that the "bony structure of the ribs was cut with the greatest ease, and that the bodies of the vertebrae were capable of being sliced off with a knife." Bence Jones concluded from the chemical properties of this urinary substance that it was "an oxide of albumen, and from the ultimate analysis it is the hydrated deutoxide of albumen." He also

suggested that this substance should be looked for in further cases of "mollities ossium" and prophesied that the explanation of its formation might lead to "the comprehension of the nature of the disease which affects the bones." This protein is now known as Bence Jones protein and the disease with which it is commonly associated, multiple myeloma. One year later, in 1846, Dalrymple² published an article on the "microscopical character of mollities ossium." In this article he described the gross appearance of the diseased bone, recognized the replacement of bone by "nucleated cells," and correctly suspected the malignant nature of the disease. In 1850 MacIntyre³ reported at length the case of Watson and Bence Jones. His description of the symptomatology of the disease is as accurate today as it was almost 100 years ago. Von Rustizky⁴ first described the condition under the name of "Multiple Myelome" in 1873 but it was not until 1889 that Kahler⁵ ascribed the four cardinal findings to this disease, i.e. bone pain, deformation and abnormal fragility of bone, cachexia and the presence of Bence Jones proteinuria. Ten years later Ellinger⁶ first noted the interrelationship of hyperproteinemia and multiple tumors of bone. This important work was corroborated by Jacobson⁷ in 1917 and by many others since that time. Longworth, Shedlovsky and Mac-

* From the Departments of Medicine and Radiology, University of Rochester School of Medicine and Dentistry, and the Medical Clinics of the Strong Memorial Hospital and the Rochester Municipal Hospital, Rochester, N. Y. Expenses were defrayed in part by a grant from the American Cancer Society.

† Present address: Department of Medicine at the University of California at Los Angeles.

Innes⁸ were the first to make electrophoretic studies in cases of multiple myeloma and pointed out the existence of unusual patterns in this condition.

INCIDENCE

Plasma cell tumors are rare but are probably not nearly so rare as they have

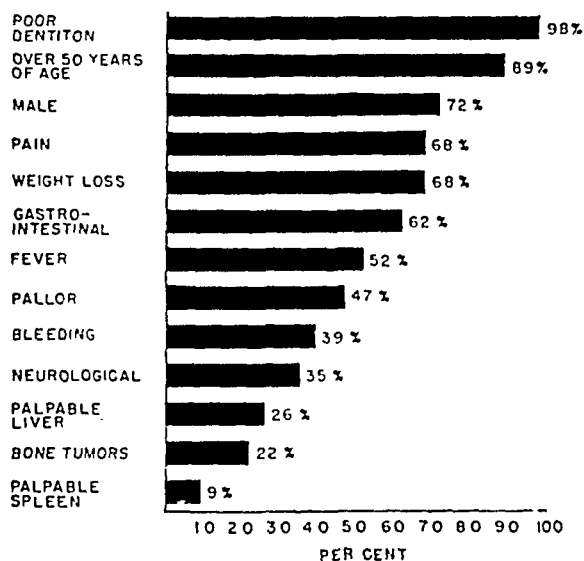


FIG. 1. Signs and symptoms of sixty-one cases of multiple myeloma.

been reported in the past. At this clinic they represented 0.02 per cent of all hospital admissions and 0.66 per cent of all malignancies. It is interesting to note that from 1926 to 1936 the incidence of multiple myeloma was 1.4 cases per 10,000 hospital admissions, and from 1936 to 1946, 2.8 cases per 10,000 hospital admissions. Doubtless this two-fold increase is due to a variety of causes perhaps the most significant of which has been the electrophoretic study of plasma proteins. More expert hematologic and pathologic examination of the blood and blood-forming tissues has also played a prominent part in this apparent increase. Then, too, greater numbers of people are entering the fifth, sixth and seventh decades of life than ever before and it is during these decades that myeloma is most common.

CLINICAL FINDINGS

The signs and symptoms which were noted in sixty-one cases of multiple myeloma

are summarized in Figure 1. They will be discussed in order of frequency.

Poor Dentition (98 per cent). Surprising as it may seem the commonest clinical finding was a pronounced carious condition or a complete absence of teeth. It is realized that the majority of normal people in this age group have either total or partial loss of teeth. However, it seems outside the realm of chance that practically all cases of multiple myeloma should show this unless there were some other factor which predisposed to dental softening. The purely speculative hypothesis is offered that the same process which so commonly leads to skeletal osteoporosis also affects the teeth and leads to their premature decay and removal.

Age. It is a well established fact that this disease is most prevalent in the older age groups. However, well authenticated cases have been reported in children and infants,⁹ but these cases must be regarded as medical curiosities. The average age of patients with multiple myeloma in this group was fifty-eight years, 89 per cent of all patients being over fifty years of age at the time of admission to the hospital. The extremes of age were thirty-one and seventy-six years.

Sex. The male sex is more commonly affected than the female. The reasons for this are not clear. Bone trauma, to which the male is more often exposed, has been implicated as an important predisposing factor by some. In our experience the disease was seen two and one-half times more frequently in the male than in the female. The answer to this observed fact must await further investigation.

Pain (68 per cent). Any description of multiple myeloma would be incomplete without reference to the pain which commonly accompanies the disease. The pain is of two types: that due to bone pain *per se* and that due to fracture of bone. The bone pain may begin insidiously, sometimes being remittent in type resembling "rheumatic pains." These pains usually progress and terminate in agonizing spasms. The

latter are best described by those who have experienced them: "My muscles feel like they are being torn from my legs," and "It feels like a steel band is being tightened about my knee." Many patients have begged the examiner not to come near the bed for fear of bringing on agonizing paroxysms of pain. The cause of this pain is not clear. It is thought that the osteolytic process taking place in the medullary cavity of the bone is responsible.

In contradistinction to the insidious onset of this type of pain there may be a sudden onset of acute pain which is usually the result of a pathologic fracture incurred by a sudden movement or the lifting of a heavy object. This pain is frequently limited to the back or the chest and may be of such severity as to cause the patient to cry out or fall to the floor.

Weight Loss (68 per cent). Early in the course of multiple myeloma weight loss is usually slight. However, as the disease progresses and particularly if uremia develops, the loss of weight becomes pronounced (averaging 29 pounds). Our patients admitted to weight loss in 68 per cent of the cases in which an adequate history could be obtained. It is surprising to us that inanition is not more extreme in view of the excessive loss of protein in the urine shown by some of our cases.

Gastrointestinal Symptoms (62 per cent). Associated with weight loss have been varying degrees of anorexia, nausea, vomiting, diarrhea and constipation. As a rule these symptoms were not distressing unless azotemia developed when, as would be expected, anorexia, nausea and vomiting were often pronounced.

Fever (52 per cent). Fever is a common accompaniment of the disease. It is usually low-grade, remittent and resembles the febrile course sometimes seen in tuberculosis. Terminally, the fever may go as high as 40° to 41°C. This terminal hyperpyrexia cannot always be explained on the basis of pneumonia or other existing infection. Its etiology remains obscure.

PHYSICAL FINDINGS

Pallor (47 per cent). By the time they seek medical care the majority of patients with myeloma are already suffering from anemia of considerable severity. The pallor (present in 47 per cent of the cases) is many times associated with a peculiar, dusky, sallow coloration which cannot be attributed to anemia *per se*. This peculiar appearance of the skin is not distinctive of myeloma for it is often seen in other malignant states.

Bleeding (39 per cent). Hemorrhage from the nose, gums, lungs, gastrointestinal tract and into the skin has been reported previously. In the majority of these cases no known defect in the clotting mechanism has been implicated. This has been true in fifteen of our cases in which bleeding was encountered and in which adequate studies including fibrinogen level, prothrombin concentration, bleeding time and platelet counts were made. However, in five of these patients with marked hyperproteinemia the clot was very friable and retracted poorly. It has been suggested by Bayrd and Heck¹⁰ that the abnormal bleeding tendency encountered in multiple myeloma may be explained on the basis of hyperproteinemia. Proof of this hypothesis must await further study.

It is important to note that in three of our patients in whom surgical procedures were carried out, profuse hemorrhage was encountered. We have no explanation of this.

Neurologic (35 per cent). Disorders of the nervous system are more commoner than one might expect. The majority of neurologic lesions in this group were an indirect result of pathologic fracture of the skeletal system. Because of the frequency of involvement of the vertebral column resulting in collapse of the vertebral bodies, root cord compression with its attendant root pain was the commonest neurologic manifestation.

Palpable Liver and Spleen. The liver and spleen were palpable in 26 and 9 per cent, respectively, of all cases. Much higher percentages have been reported but in these

cases the presence of a palpable liver or spleen was not very common.

Palpable Tumors (22 per cent). Rarely (three cases in this series) the presenting complaint was a palpable tumor attached to the bone. In general these tumors were

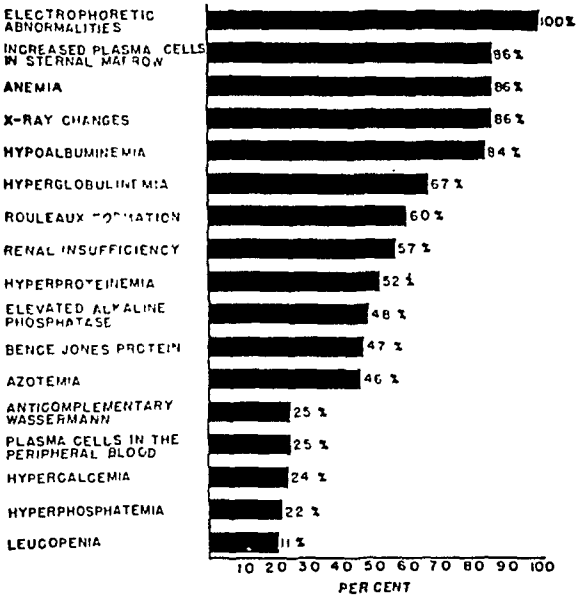


FIG. 2. Laboratory findings of sixty-one cases of multiple myeloma.

non-tender, soft, frequently pulsatile masses and were attached to the sternum, skull, ribs, clavicle or jaw.

LABORATORY FINDINGS

The laboratory findings in sixty-one cases of multiple myeloma are shown in Figure 2.

Bence Jones Protein. Despite the fact that over 100 years ago Watson, Dalrymple, MacIntyre and Bence Jones noted a peculiar urinary protein in a patient with multiple myeloma, we still know little about the origin or the physiology of this protein. Wintrobe and Buell¹¹ point out that “Bence Jones protein must be regarded as a class of substances which exhibit in common a peculiar coagulation phenomenon.”

The incidence of Bence Jones proteinuria in cases of multiple myeloma is a matter of extreme variation as reported in the literature:

Name	Per cent
Atkinson ¹²	87
Magnus-Levy ¹³	73
Geschickter and Copeland ¹⁴	65
Bayrd and Heck ¹⁰	53
Batts ¹⁵	50
This report.....	47
Gutman ²⁵	45
Ghormley and Pollock ¹⁶	35
Coley ¹⁷	8

As can be seen above the incidence of Bence Jones proteinuria in our series was 47 per cent. The marked variation in incidence of Bence Jones proteinuria is understandable when one considers the nature of this substance or substances. It has been pointed out^{13,14,18} that early in the course of such disease the appearance of Bence Jones bodies in the urine may be intermittent and may become constant only late.¹ Aside from these variables, the behavior of the protein depends on many circumstances such as the concentration of the Bence Jones protein, the pH of the urine, the concentration of urinary electrolytes, urea and albumin.

The occurrence of Bence Jones proteinuria has been reported in diseases other than multiple myeloma: metastatic carcinoma, lymphatic leukemia, myelogenous leukemia, senile osteomalacia, fibrocystic disease, multiple fractures of bone, inactive pulmonary tuberculosis, etc.

A rough test for the presence of Bence Jones protein is the sulfosalicylic acid test which is carried out as follows: To 1 cc. of clear urine add three drops of a 20 per cent solution of sulfosalicylic acid. If no cloudiness appears, protein is absent. If a cloud develops, heat the mixture to boiling and then cool. If cloudiness persists on boiling and remains on cooling, albumin and globulin are both present. If cloudiness disappears on boiling and reappears on cooling, either proteose or Bence Jones protein is probably present. If Bence Jones protein and/or albumin and globulin are present, the cloudiness does not completely disappear but becomes less dense on heating. The presence of a positive sulfosalicylic acid test for Bence Jones protein is indication for

the more laborious method of heating the urine specimen in a water bath in which the temperature is slowly raised. Attempts at establishing the existence of Bence Jones bodies in urine sometimes meet with failure because of improper attention to the method of heating the urine. We have obtained best results by heating the urine specimen in a water bath, slowly raising the temperature from 40°C. to 100°C. during a period of fifteen or twenty minutes. This slow method of heating makes it easier to discern the presence of a protein in the urine specimen and at what temperature it precipitates or disappears. A cloudiness appearing at a temperature of 45°C. to 65°C., disappearing on boiling and reappearing on cooling at 65° to 85°C. indicates the presence of Bence Jones protein. If albumin is also present, confusion may result. This may sometimes be avoided by filtration of the urine specimen while boiling, thus removing the coagulated albumin from solution and leaving the Bence Jones protein in the filtrate. Subsequent heating and cooling of the filtrate as noted above may then be carried out and the existence of Bence Jones protein established or disproved.

The term *Bence Jones protein* does not refer to a single chemical entity but to a group of proteins with closely related properties. According to Bayne-Jones and Wilson²² there are at least three immunologically distinct types of this protein, and Hektoen and Welker²³ have reported two cases in which two of these types were excreted in the urine simultaneously. Moore et al.²⁴ have found widely different electrophoretic mobilities for urinary Bence Jones protein from different patients. This is in accord with our experience. These authors have confirmed the observation of Svedberg²⁰ that protein specimens from different patients give sedimentation constants ranging from 2.8 S to 3.7 S. In spite of these variations the generally accepted values for the molecular weight of Bence Jones protein are 35,000 to 37,000.^{19,20,24}

Bence Jones protein has been obtained in crystalline form at least fourteen times but,

as Magnus-levy²¹ has shown, it is frequently very difficult or apparently impossible to crystallize, perhaps because it may be excreted in combination with a pseudoglobulin. Sometimes crystallization is difficult or impossible because of the presence in a single urine of two different varieties of Bence Jones protein. In one case observed by the others, the urine regularly contained large and nearly equal amounts of two proteins migrating during electrophoresis as separate peaks of slightly different mobility. When these proteins were separated from each other in nearly pure form, the solutions of each were found to display in identical manner the well known temperature-solubility relationships of Bence Jones protein. All attempts at crystallization failed.

Plasma Proteins. Elevated total plasma protein (over 8.0 Gm. per cent by modified Howe technic) occurred in 52 per cent of our cases. The highest level was 13.4 Gm. per cent; the lowest 5.0 Gm. per cent. Hyperglobulinemia was present in 67 per cent. It is important to remember that because of a lowered albumin level, the hyperglobulinemia may be present without hyperproteinemia. (Table 1.)

Gutman et al.²⁵ and Snapper²⁶ have reported that on the basis of Howe fractionation studies all cases of multiple myeloma in which hyperglobulinemia is present fall into the following four categories listed in order of diminishing frequency: (1) Elevated euglobulin (plus pseudoglobulin I); (2) elevated pseudoglobulin I; (3) elevated pseudoglobulin I and II; (4) elevated pseudoglobulin II. These authors have also studied the globulin distribution in the following diseases associated with hyperglobulinemia: Lymphogranuloma venereum, sarcoid, cirrhosis, kala-azar, disseminated lupus, subacute bacterial endocarditis, leprosy, tubercular lymphadenitis, rheumatoid arthritis, leukemia, chronic nephritis and a few miscellaneous infections. All of these cases were found to belong in group 1. It therefore follows that whenever hyperglobulinemia of groups 2, 3 or 4 is present, the disease is probably multiple myeloma. Fractionation

is of no diagnostic aid when the findings place it in the first category.

Gutman *et al.*²⁵ have pointed out that in some cases of multiple myeloma the conventional Howe fractionation technic may yield albumin values that are grossly too

are reported twelve new cases studied by electrophoresis. In four of these cases there was an abnormally large γ peak, which in two instances was associated with a small peak referred to as an M component migrating with the mobility of fibrinogen. Three

TABLE 1

LABORATORY FINDINGS IN SIXTY-THREE CASES OF PLASMA CELL TUMORS

	Normal	Elevated	De-pressed	Not Done	Highest Values	Lowest Values	Average
	No. of Cases						
White blood count.....	45	10	7	1	51,200 per cu. mm.	3,000 per cu. mm.	8,075 per cu. mm.
Red blood count.....	9	..	51	3	6.1 million per cu. mm.	1.46 million per cu. mm.	3.09 million per cu. mm.
Hemoglobin.....	9	..	54	..	15.5 Gm. %	5.1 Gm. %	9.8 Gm. %
Serum calcium.....	30	11	4	18	19.9 mg. %	6.2 mg. %	11.0 mg. %
Serum phosphorus.....	32	10	3	18	10.5 mg. %	2.1 mg. %	4.4 mg. %
Total plasma proteins.....	22	27	3	11	13.4 Gm. %	5.0 Gm. %	8.4 Gm. %
Serum albumin.....	8	0	43	12	5.6 Gm. %	1.0 Gm. %	3.5 Gm. %
Serum globulin.....	16	34	1	12	11.4 Gm. %	1.0 Gm. %	5.0 Gm. %
Non-protein nitrogen.....	31	26	..	6	285 mg. %	62 mg. %

high, but that in these instances more protein may precipitate with the globulin fraction if a longer time is allowed before filtration.

Since our belief is that electrophoresis is the method of choice, we have not fractionated the globulins by the Howe method in our cases.

ELECTROPHORETIC STUDIES

The value of electrophoresis in the diagnosis of multiple myeloma was first revealed in 1939 by Longworth, Shedlovsky and MacInnes⁸ who found rather characteristic abnormalities in two cases and normal patterns in one case. In 1940 Kekwick²⁷ published the results of combined electrophoretic and ultracentrifugal studies in five cases. The most extensive studies reported have been by Gutman *et al.*²⁵ and Moore *et al.*²⁴ The latter paper deals at length with the problem of Bence Jones proteinemia and the relation of Bence Jones protein to the abnormal peaks in the electrophoretic patterns. In these two papers there

cases showed a large β peak, two a large M peak and one a small M peak. In two cases the patterns were described as normal.

On the other hand, we have encountered no normal patterns in thirty-three consecutive cases, the first twenty-nine of which are described in this paper. We ascribe the discrepancy in these findings to two factors: (1) Our use of the 2:1 dilution of plasma by sodium-barbital buffer as advocated by Longworth in 1942²⁸ and (2) the use of the tall form of the Tiselius cell with a wider spread of the electrophoretic peaks. Under these conditions small abnormalities are revealed which would otherwise not be apparent. These abnormalities, while small, are reproducible and significant.

Methods of Electrophoresis. Plasma was used in all cases although occasionally additional patterns were obtained from serum.

In order to demonstrate small irregularities, the high dilutions of plasma frequently recommended were avoided. The plasma was diluted with an equal volume of veronal

TABLE II
ELECTROPHORETIC FINDINGS IN THIRTY CASES OF PLASMA CELL TUMOR

Case No.	Interval after First Sample	Urinary Bence Jones Protein	Mobility of Abnormal Peak	Protein Concentrations in Gm. Per Cent							Remarks	
				Ab-normal Peak	Total	Al-bum	Alpha ₁	Alpha ₂	Beta	Phi*		Gamma
1	0	Less than gamma	2.4+	8.1+	3.1	0.2	0.8	0.8	0.5	0.2	After stilbamidine therapy * Value from ascending pattern is 0.30
1	2 mo.	0	Less than gamma	2.4+	7.4+	2.5	0.3	0.8	0.7	0.4	0.3	
2	0	Less than gamma	2.3+	7.9+	3.0	0.4	0.8	0.9	0.3	0.3	
3	0	Less than gamma	5.5+	11.8+	3.1	0.5	1.3	0.6	0.8*	0.0?	
4	0	Less than gamma	2.4+	8.0+	3.2	0.4	0.6	0.6	0.8	0.0?	* Value from ascending pattern is 0.30
4	1 mo.	0	Less than gamma	2.4+	7.5+	2.6	0.5	0.7	0.8	0.4	0.0?	
5	0	Less than gamma	2.9+	8.4+	3.2	0.3	0.7	0.7	0.4	0.1	
6	+	Less than gamma	2.6+	8.6+	2.9	0.5	1.0	0.7	0.4	0.4	
7	+	Equal to gamma	2.3	8.0	3.1	0.4	0.8	0.6	0.7*	2.3	* Value from ascending pattern is 0.47 During lobar pneumonia After pneumonia
8	0	Equal to gamma	2.3	7.8	2.2	0.6	0.9	1.1	0.8	2.3	
9	0	Equal to gamma	5.9	9.5	1.7	0.3	0.6	0.5	0.5	5.9	
9	3 wk.	0	Equal to gamma	5.3	8.9	1.6	0.3	0.6	0.5	0.5	5.3	
9	1 yr.	0	Equal to gamma	4.1	8.5	2.2	0.3	0.6	0.6	0.6	4.1	* Value from ascending pattern is 0.87
10	0	Equal to gamma	3.0+	9.9+	2.2	0.7	1.2	1.0	1.7*	3.0	
11	0	Equal to gamma	6.2	11.1	3.3	0.3	0.5	0.4	0.4	6.2	
12	+	Between phi and gamma	2.9+	5.2+	1.4	0.1	0.3	0.5	2.9+		
13	+	Between phi and gamma	7.2	10.4+	1.9	0.3	0.6	0.4	7.2+		0.2
14	0	Equal to phi	2.4+	6.8+	2.5	0.5	0.8	0.5	2.4+		
15	0	Equal to phi	4.1	8.9	3.0	0.4	0.7	0.6	4.1		
16	0	Equal to phi	5.7	8.7	1.7	0.4	0.7	5.7	0.1	
17	0	Between beta and phi	6.5+	9.6+	2.1	0.3	0.6	6.5+	0.1	Plasma cell leukemia Hepatic cirrhosis Bump slightly larger Bump still larger 2 days before death 1 day postoperatively solitary myeloma of antrum
18	+	Equal to beta	4.8+	10.2+	3.6	0.6	1.0	4.8+	0.3	
19	0	Equal to beta	7.9+	11.8+	2.1	0.4	0.6	7.9+	0.6	0.2	
20	+	Equal to beta	6.1	9.0	2.3	0.3	6.1	0.3	0.1	
21	+	Equal to beta	6.3+	8.9+	1.8	0.5	6.3	0.2	0.2	
22	+	Between phi and gamma	?	7.0	3.2	0.5	0.8	0.7	1.8		
23	+	Sharp gamma	6.4	3.5	0.5	0.8	0.7	0.5	0.4	
24	+	Sharp gamma	8.1	3.8	0.6	1.2	0.9	0.6	0.9	
25	+	Sharp gamma	6.3	3.2	0.5	1.0	0.8	0.3	0.4	
26	+	Less than gamma	0.1	5.9	3.2	0.5	0.9	0.6	0.4	0.2	
27	+	Bulge on phi	6.4	4.2	0.2	0.7	0.7	0.5	0.1	
28	?	Bump on gamma	6.1	3.0	0.4	1.1	0.8	0.4	0.4	
28	3 mo.	0	Bump on gamma	6.8	3.5	0.5	1.2	0.9	0.3	0.5	
28	11 mo.	0	Bump on gamma	7.2	4.0	0.3	1.0	0.8	0.6	0.5	
29	+	Bump on gamma	6.5	2.1	0.9	1.2	1.1	0.8	0.4	
30	0	Bump on gamma	7.4	2.8	0.8	1.1	1.0	1.0	0.6	
30	7 mo.	0	Bump on gamma	6.9	3.2	0.4	0.8	0.9	0.7	0.8	
Normal average (20 plasmas)				6.9	4.1	0.4	0.6	0.8	0.3	0.7	

* Represents fibrinogen plus a small amount of gamma globulin.

buffer of pH 8.5 and ionic strength 0.1. This diluted plasma was dialyzed in a cellophane sac against 2 L. of the veronal buffer. Mechanical rocking in the refrigerator permitted satisfactory equilibration in sixteen hours.

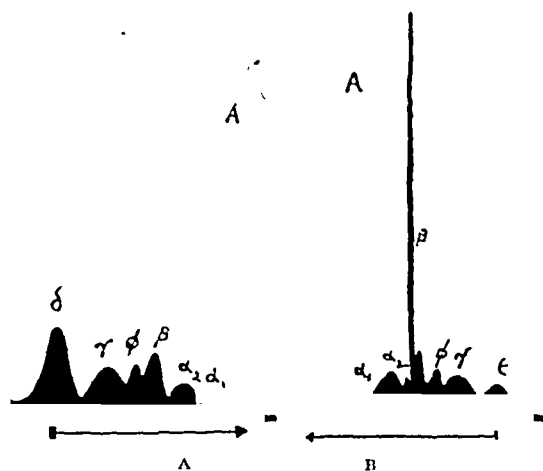


FIG. 3. Ascending (left) and descending (right) patterns of normal human plasma.

Electrophoresis was carried out in the tall form of the standard 11 ml. Tiselius cell at a field strength of about 6.8 volts per cm. at a water bath temperature of 1°C. The current was passed for at least three hours. The patterns were photographed by the scanning method of Longworth²⁹ and the areas of the peaks were obtained from photographic enlargements by the use of a planimeter. If the Tiselius cell with a double center section is employed, the spread of the peaks is too small to reveal some important details. A more complete account of the methods may be found in a previous paper.³⁰

Because of the 2:1 plasma dilution routinely employed, many of the large abnormal peaks extended beyond the range of the photographic plate. This made it impossible to measure the area of such a peak although in some instances its height was determined by measuring the distance in the plane of the schlieren diaphragm between the undeviated slit image and the most deviated image and multiplying by three. We preferred to sacrifice an accurate determination of the area of large abnormal peaks in order to stabilize small peaks by a

higher density gradient and to increase slight irregularities. Higher dilutions give patterns which more accurately reflect the concentrations of the plasma constituents but this theoretic gain is offset by a practical loss.

Results of Electrophoresis. In Table II and in descriptions of some of the patterns we frequently refer to "abnormal" peaks. This is unfortunately an ambiguous term. An "abnormal" peak may indicate either the presence of an abnormal concentration of a normal plasma constituent or the presence of a protein not found in normal plasma.

The results of these electrophoretic studies may best be divided into four groups according to the type of pattern present: (1) major abnormal patterns showing tall, narrow peaks, twenty-one cases; (2) minor abnormal patterns showing slight irregularities, eight cases; (3) normal patterns from one case of solitary myeloma; (4) abnormal patterns which might be confused with multiple myeloma, five cases. For comparison with these and subsequent patterns, normal patterns are shown in Figure 3.

1. The first twenty-one cases of plasma cell tumors are tabulated in the order of increasing mobility of the abnormal peak (Table II) which varied from slower than gamma to as fast as beta.* The patterns of this group all showed narrow, tall peaks, usually so tall that they extended beyond the edge of the photographic plates. In this group of twenty-one cases the mobilities of the abnormal peaks showed the following distributions: less than gamma in six cases; equal to gamma in five cases; between gamma and fibrinogen in two cases; equal to fibrinogen in three cases; between fibrinogen and beta in one; equal to beta in four. Figure 4 shows the patterns from Case 17 illustrating an abnormal peak migrating between fibrinogen and beta. Space does not permit showing patterns illustrating all

* An article recently published reports two cases with large abnormal peaks migrating with the mobility of alpha₂ globulin. WUHRMANN, F., WUNDERLY, C. and WIEDEMANN, E., *Ueber das Alpha-Globulin-Plasmocytom.* *Schweiz. med. Wchnschr.*, 78: 180, 1948.

the various mobilities which have been frequently reported for these characteristic tall, narrow peaks. A single example of a frequently reported type of pattern is shown in Figure 4.

Figure 5 from Case 6 shows a peak migrat-

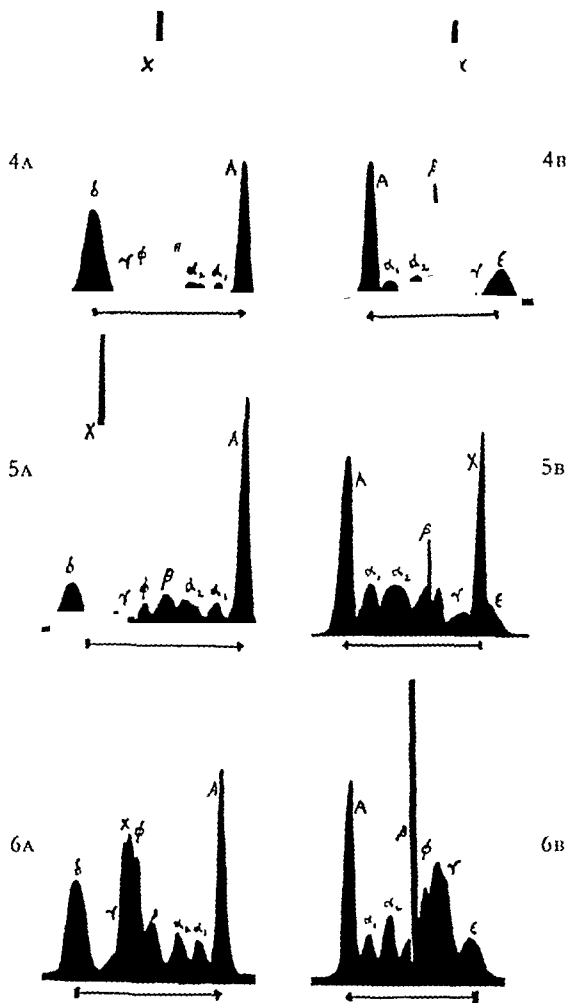


FIG. 4. A and B, major abnormality (Case xvii, multiple myeloma) migrating between fibrinogen and beta globulin.

FIG. 5. A and B, major abnormality (Case vi, multiple myeloma) showing a peak migrating slower than gamma globulin.

FIG. 6. A and B, major abnormality (Case viii, multiple myeloma); abnormal gamma peak is of intermediate height.

ing more slowly than gamma globulin (not previously reported to our knowledge). This example is chosen because it shows a curious phenomenon. The current was passed for thirty minutes longer than the usual three hours. During the last twenty minutes the gamma peak in the ascending pattern

split into two components. The low gamma concentration is noteworthy.

Figure 6 shows the patterns of Case 8. They are somewhat atypical in that abnormal gamma peak is of intermediate height.

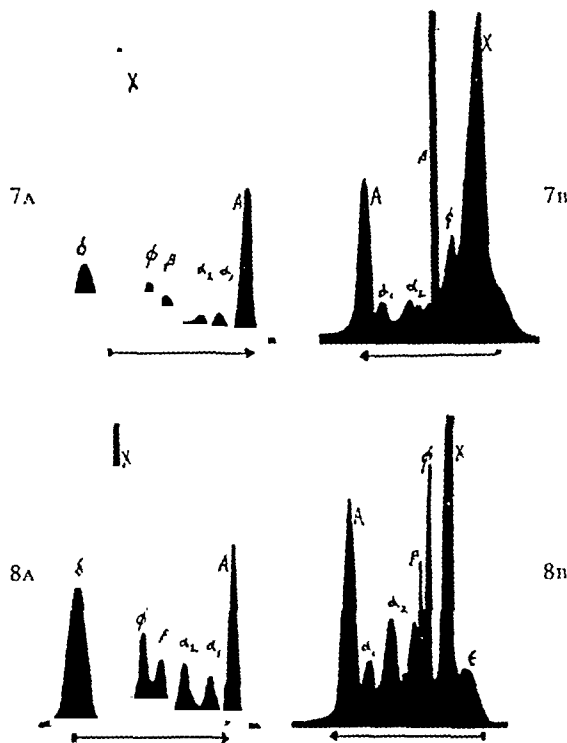


FIG. 7. A and B, major abnormality (Case ix, multiple myeloma and lobar pneumonia); note broad gamma peak.

FIG. 8. A and B, major abnormality (Case x, multiple myeloma given massive roentgen treatment); note increase in all globulins and the difference in height of the fibrinogen peak in the ascending and descending patterns.

Figure 7 shows the patterns from Case 9 taken during coincident lobar pneumonia. This is an atypical and ambiguous pattern. The unusual feature is the width of the gamma peak in relation to its height. Subsequent patterns after recovery from pneumonia showed some changes in peak areas but the gamma remained broad for its height. It is possible that chronic hepatitis was present. These patterns are practically identical with those seen in one fatal case of subacute hepatitis. The patterns are so similar that it is unnecessary to show them both. We have patterns from fifty-nine other cases of hepatic disease, but these are

the only pair which might be confused with those seen in multiple myeloma. The failure of α_1 , α_2 and fibrinogen to rise in Case 9 during lobar pneumonia is worthy of note.

Figure 8 shows the patterns of Case 10;

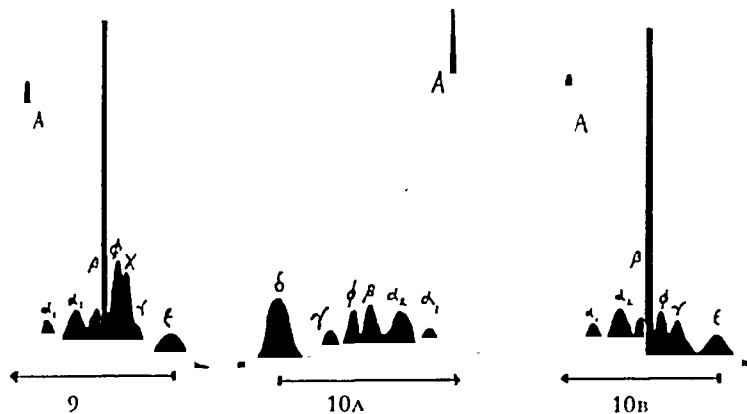


FIG. 9. Intermediate abnormality (Case xxiii, multiple myeloma); note small peak migrating close to gamma globulin.

FIG. 10. A and B, minor abnormality (Case xxii, multiple myeloma); note relatively sharp small gamma peak.

they are very unusual. While the abnormal gamma peak is tall and sharp, the other globulin peaks are all increased. The

after his disease was recognized and during these years received roentgen radiation totaling 30,000r.

2. The eight patterns from Cases 22 to 29 are of special interest because they are of a type not hitherto reported in multiple myeloma. These abnormalities would probably pass unnoticed if the plasma were diluted four to one, or if the Tiselius cell with the double center section were employed. (The small abnormalities are much more obvious in the photographic enlargements than in the reduced figures shown here.)

Case 22 shows a small abnormal peak. (Fig. 9.) This pattern is intermediate in type between the first twenty-one and the following seven.

The patterns of Cases 23, 24 and 25 are shown in Figures 10, 11 and 12, respectively. In these three cases the gamma peaks, while not large, are sharp instead of being rounded as in the normal. In Case 24 the other globulin peaks are sufficiently elevated to produce a moderate hyperglobulinemia. In our experience this type of peak was encountered in only one disease other than myeloma. This exception was a case of

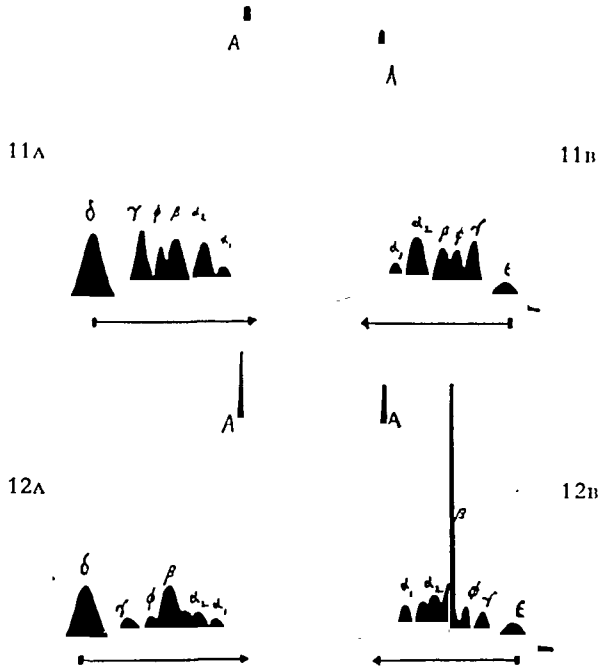


FIG. 11. A and B, minor abnormality (Case xxiv, multiple myeloma); note sharp gamma peak and moderate hyperglobulinemia.

FIG. 12. A and B, minor abnormality (Case xxv, multiple myeloma); note sharp gamma peak particularly in the descending pattern.

adenocarcinoma of the stomach with metastases to the esophagus, liver and regional lymph nodes. The patterns from this case are shown in Figure 13. It will be seen that in the ascending pattern the gamma peak is abnormally sharp and is more irregular than in the three cases of multiple myeloma.

In Case 26 (Fig. 14) the descending pattern shows a small bump migrating more slowly than gamma. We have seen no other pattern like this.

Case 27 (Fig. 15) is a "plasma cell leukemia." The gamma is very low. In the ascending pattern an abnormal bulge is seen on the gamma side of the fibrinogen peak. The mobility of this bulge is the same as that of the pure Bence Jones protein peak in the patient's urine.

There are two striking features in the electrophoretic pattern of Case 28 (a case of hepatic cirrhosis and multiple myeloma). The patterns shown in Figure 16 were obtained from a plasma sample taken eleven months after the initial sample. During this time the albumin concentration rose to normal levels (a low albumin is the most common single finding in malignant disease) and the small irregularity on the leading edge of the gamma peak became more pronounced. We have encountered a small irregularity in this location (ascending pattern) only in malignant disease (16 per cent of 275 cases), acute infections such as pneumonia and pneumococcal meningitis, immediately following surgical operation and in six cases of multiple myeloma.

Figure 17 shows the ascending pattern from Case 29. There is a similar irregularity on the leading edge of the gamma peak. All the globulin peaks except gamma are increased. This patient was admitted to the hospital in uremia and the blood sample was taken two days before death.

3. Case 30 is one of solitary myeloma of the antrum. The first patterns show abnormal elevations of all the globulins except gamma. These abnormalities were probably the result of surgical exploration of the antrum which was done the day before the blood sample was taken. During

this operation a massive hemorrhage occurred. The patterns from a blood sample taken seven months later were normal except for a rather low albumin and an elevated fibrinogen. These abnormalities were probably due to the infection associated

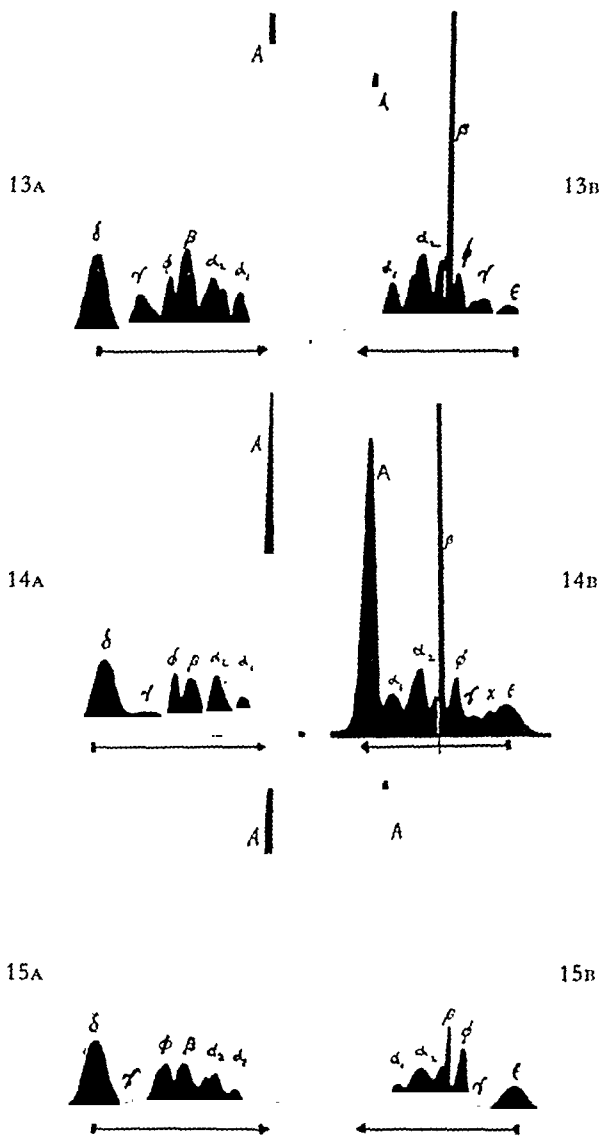


FIG. 13. A and B, pattern from a case of adenocarcinoma of the stomach with metastases to the esophagus, liver and regional lymph nodes; note similarity to the patterns in Figures 10, 11 and 12.

FIG. 14. A and B, minor abnormality (Case xxvi, multiple myeloma); note small bump migrating slower than gamma globulin in the descending pattern.

FIG. 15. A and B, minor abnormality (Case xxvii, "plasma cell leukemia"); note low gamma globulin and the abnormal bulge on the gamma side of the fibrinogen peak in the ascending pattern.

with a persistent draining sinus tract at the site of operation. Since widespread disease was probably absent as indicated by bone marrow studies, it is not surprising that these patterns showed none of the abnor-

malities which are suggestive of multiple myeloma.

In the first twenty-one cases (except Case 18) the plasma albumin level was below normal and often very low. The average value for this group was 2.5 Gm. per cent. In the entire series of sixty-three cases the albumin concentration as determined by the Howe method was below normal in 86 per cent.

Special attention should be drawn to the fact that the concentration of gamma globulin was usually very low unless the abnormal peak migrated with a mobility equal to or close to that of gamma globulin in which event we have no way of measuring the concentration of normal gamma globulin. It may be that a low concentration of normal gamma globulin is a constant and important feature of multiple myeloma.

4. We have five instances in which patterns showed abnormalities which might falsely suggest multiple myeloma. (Figs. 6, 13, 18, 19 and 20.) The patterns in Figure 6 are almost identical with those seen in one case of hepatitis and are therefore not reproduced. Figure 13 is from a case of gastric malignancy. Figure 18 shows the ascending pattern from the serum of a case of hepatic cirrhosis. There is evidently an abnormal peak migrating with the mobility of fibrinogen. It is not well separated from the large, broad gamma peak so commonly found in cirrhosis. This peak is probably not due to residual fibrinogen since the

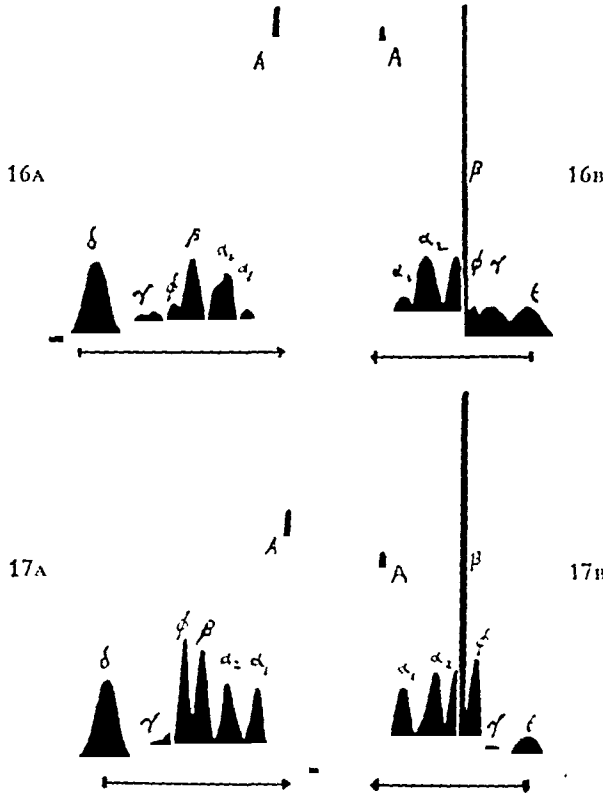


FIG. 16. A and B, minor abnormality (Case xxviii, multiple myeloma and cirrhosis); note the small irregularity on the leading edge of the gamma peak (ascending pattern).

FIG. 17. A and B, minor abnormality (Case xxix, multiple myeloma); note the small irregularity on the leading edge of the gamma peak (ascending pattern) and the elevation of all the globulin peaks except gamma.

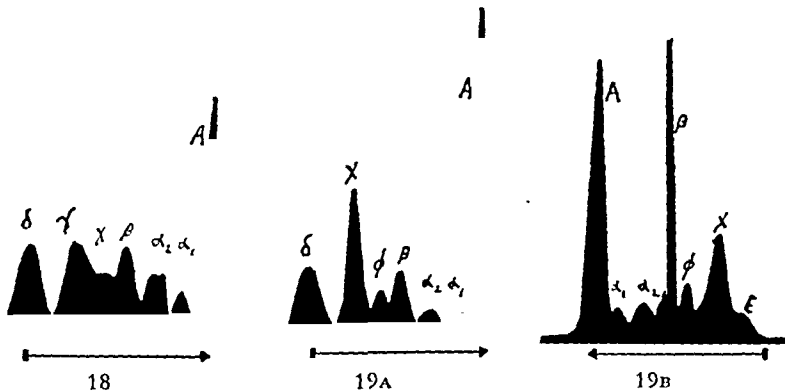


FIG. 18. Ascending pattern from the serum of a case of hepatic cirrhosis; note abnormal peak migrating with the mobility of fibrinogen.

FIG. 19. A and B, patterns from a case of degenerative arthritis; note abnormal gamma peak.

addition of thrombin failed to remove it. A similar pattern is reported by Stern and Reiner³¹ in a case of cirrhosis. Even though this pattern shows an abnormal peak, we do not believe it could be confused with a pattern of multiple myeloma. Figure 19 shows the patterns from a patient who presented old degenerative arthritic changes in one humerus and both femoral heads. The blood serum showed an anomaly in that the cephalin flocculation reaction was one plus while the thymol turbidity reading was 169 units. The sternal marrow was normal. It is of course possible that this is an early case of myeloma. A second set of patterns taken six months later showed no change. Figure 20 shows the pattern from a patient who had wide spread bone and pulmonary metastases from a carcinoma of unknown primary site. This patient died in another hospital and no autopsy was performed. It seems unlikely, however, that he had multiple myeloma although we have recently seen an almost identical pattern in a case which was found at autopsy to have this disease. Increased experience may or may not permit the differentiation of such patterns.

Discussion of Electrophoretic Results. Ultracentrifugal and diffusion studies^{27,32,33,34} have shown that the large abnormal peaks in the patterns of multiple myeloma are usually due to proteins of high molecular weight (160,000–200,000) but may occasionally be due to low molecular weight proteins, probably Bence Jones proteins.

Moore *et al.*²⁴ studied the sera of seven cases of multiple myeloma by the Howe fractionation method, electrophoresis and the ultracentrifuge. In two of these cases Bence Jones protein was demonstrated in the plasma by immunologic methods. Both of these cases were excreting this protein in the urine. In another case without Bence Jones proteinuria the presence of this protein in the plasma was indicated by ultracentrifugal studies. The many interesting findings reported by these authors cannot be reviewed in detail. One of their conclusions is that in "many (probably the

majority of) cases of multiple myeloma with marked hyperglobulinemia" only a very small proportion of the excess of globulins is Bence Jones protein.

Sedimentation diagrams of the high molecular weight proteins are often similar

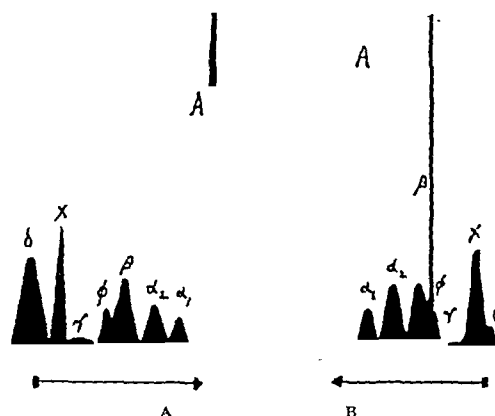


FIG. 20. A and B, patterns from a case of widespread osseous metastases from a carcinoma of unknown primary site.

to those of normal gamma globulin but are sometimes very different, corresponding to no known constituent of normal plasma. It is well known that proteins may have similar electrophoretic mobilities and sedimentation characteristics and yet be different chemically. This fact usually makes it impossible to determine by these two means alone whether a given protein is abnormal or not. The large peaks in the first six cases in Table II probably represent abnormal proteins since there is no detectable protein in normal plasma which migrates more slowly than gamma globulin. It is curious that a peak migrating more slowly than gamma has not to our knowledge been previously reported in multiple myeloma. The probable explanation lies in the fact that most of the earlier electrophoretic studies of multiple myeloma were made with buffers in which the normal gamma peak did not migrate away from the boundary anomaly.

With the exception of Case 9, all of the abnormally large peaks with the mobility of gamma globulin were too narrow to be confused with the large gamma peaks produced by diseases other than myeloma.

Such diseases include hepatitis (acute and chronic), disseminated lupus, lymphogranuloma venereum, kala-azar, tuberculosis, amyloidosis, scleroderma and monocytic leukemia. The narrowness of the myeloma peaks probably indicates that the proteins are more homogeneous than those comprising gamma globulin. This is not surprising in view of the large number of antibodies contained in the gamma globulin fraction.

In order to reveal this important difference in width of peaks it is essential to employ the tall form of the Tiselius cell and to continue electrophoresis until the albumin peak has migrated about 5 cm. in the cathode limb of the cell.

Wintrobe³⁵ has commented on the higher incidence of Bence Jones proteinuria when hyperglobulinemia is absent. We have found a similar difference in our two main groups of cases. In the first twenty-one cases, all of which showed large abnormal peaks, urinary Bence Jones protein was detected only seven times, an incidence of 33.3 per cent. In the group containing the next eight cases, all of which showed small abnormalities, urinary Bence Jones protein was found in seven and may have been present on one occasion in the eighth. It is plausible to suggest that at least some of the small abnormalities were due to Bence Jones protein in the plasma. This is especially likely in Cases 22, 23, 24, 25 and 27. In several of these cases the urine showed no protein other than Bence Jones protein and electrophoretic patterns of the urine showed a single peak of the same mobility as the small abnormal peaks in the plasma. If a Bence Jones protein were present in the plasma uncombined with other protein, it should appear in the urine because of its small molecular size. Moore *et al.*²⁴ have suggested that complex formation with a high molecular weight protein may prevent the escape of Bence Jones protein through the kidney. This hypothesis is attractive to us. The lack of symmetry between the ascending and descending patterns in Cases 3, 7 and 10 suggests such complex forma-

tion. This hypothesis would partially explain the high incidence of Bence Jones proteinuria in the eight cases, 22 through 29. These cases did not have any large amount of abnormal, high molecular weight protein to bind the Bence Jones protein.

The problem of the origin of Bence Jones protein and the high molecular weight proteins is totally obscure. There is no direct evidence that Bence Jones protein is produced by plasma cells. In our experience whenever this protein is found in the urine, plasma cells are found in excess numbers in the bone marrow or other tissues. Magnus-Levy believed that the large amount of protein occasionally produced (30 to 70 Gm. in twenty-four hours) could not be produced by the relatively small mass of tumor tissue. However, this objection has lost its force since it is now known that the disease is a diffuse one in which bone marrow is widely involved. It is also well to point out that the volume of the bone marrow is surprisingly large; as reported by Fairman and Whipple,³⁶ it is equal to two-thirds the volume of the liver in dogs.

In our series of cases we have found no apparent correlation between the number and morphology of plasma cells in the sternal marrow and the presence or absence of hyperglobulinemia, or the electrophoretic mobility of the abnormal peaks.

Increased Plasma Cells in Sternal Marrow (86 per cent). In few other hematologic disorders is the sternal puncture of more help in making a diagnosis than in multiple myeloma. As a rule, by the time signs and symptoms are present the disease is already far advanced and the sternum infiltrated with plasma cells. Bone marrow biopsy and/or puncture of the sternum were carried out in thirty-six cases in this series. In only five cases were the results of examination of material taken from the sternum equivocal. These five cases were later proved to be multiple myeloma by examination of material taken from other bony sites or at postmortem examination. The average per cent of plasma cells in the

sternal marrow in thirty-one cases of myeloma was 36.2 per cent. The greatest per cent of cells was 83.6 per cent, the least 6.7 per cent. These cells appear to stem from one common line—the plasma cell line (no cases of myeloma have been seen by us in which the plasma cell or its precursors was not the invading cell). It is true that these cells present a somewhat variable morphologic picture but it seems plausible that this difference in appearance may be due to differences in age. In some cases of multiple myeloma the most frequent cell seen (Wright's stain) is a large cell 20 to 30 $m\mu$ in diameter with a dark blue, somewhat scroll-like cytoplasm which contains no granules. The nucleus is round or oval and may occupy three-fourths to four-fifths of the entire cell. Its chromatin is evenly distributed throughout the nucleoplasm. There may be as many as three or four nucleoli contained within the nucleus. Mitotic figures are common. There are all gradations from this "malignant" type of cell down to the "typical" plasma cell. This latter cell measures 7 to 12 $m\mu$ in diameter. The cytoplasm is dark blue and gathered in homogeneous knots. The nucleus is placed eccentrically and fills less than one-half the cell volume; its chromatin is condensed, many times appearing pyknotic. The most characteristic feature is the appearance of the cytoplasm which, if once clearly recognized, is almost unmistakable. In fact in certain of our bone marrow preparations fragments of the cytoplasm were often seen which had evidently been broken from a myeloma or plasma cell, but which remained clearly recognizable. The presence of these cells in greater numbers than 2 to 3 per cent is considered to be abnormal, and when present in large numbers, to be diagnostic of multiple myeloma. It is the preference of this clinic to obtain both sternal aspiration and bone marrow biopsy material so that the hematologist and pathologist may collaborate in the diagnosis. It should be remembered that certain cases of multiple myeloma show a patchy plasma cell in-

filtration of the bone marrow and that it is possible in these cases to be misled by the results of sternal aspiration. A low percentage of plasma cells in material aspirated from the bone marrow does not necessarily rule out the diagnosis of multiple myeloma.

Anemia (86 per cent). The red blood count was depressed in 81 per cent of the cases. The average count was 3.09 million per cu. mm., the extremes being 1.46 and 6.1 million per cu. mm. It should be noted, however, that the anemia, although a fairly constant finding, was seldom extreme as, for example, in pernicious anemia. The anemia was usually normocytic and normochromic in type although in 14 per cent of the cases there was a macrocytosis. Only infrequently was the macrocytosis so pronounced that the diagnosis was confused with pernicious anemia.

Just as with the red blood count, the hemoglobin values were commonly depressed. In fifty-four cases (86 per cent) the hemoglobin determinations fell below 13.0 Gm. per cent and in only nine cases was the hemoglobin found to be within normal limits. The highest value recorded was 15.5 Gm. per cent; the lowest 5.1 Gm. per cent. The average hemoglobin was 9.8 Gm. per cent. It can be said that the occurrence of anemia at some stage in the course of this disease is very frequent and that the presence of the disease in the absence of anemia is distinctly unusual. The presence of unexplained anemia, particularly in the older age groups, is of great importance. Many more diagnoses of this condition will be made if more careful studies of unexplained anemias are carried out.

X-ray Changes (86 per cent). The typical findings upon x-ray examination in cases of multiple myeloma have been adequately described elsewhere. However, in the study of this group of cases certain observations have been made. The commonest (although far from diagnostic) x-ray change is one of widespread osteoporosis involving the entire skeleton. We have been struck with the uniformity of occurrence of this change and have seen cases in which this was the only

roentgenographic finding. Secondly, the occurrence of small "flea bitten" areas of rarefaction without evidence of surrounding new bone formation is not infrequent. These areas are seen in the long bones, pelvis, vertebrae, ribs and calvarium. They resemble somewhat the x-ray changes seen in leukemia. Thirdly, the most characteristic change is the appearance of the typical "punched out" area with its sharp margination without evidence of surrounding osteoblastic change. When these changes are widespread in the skull, vertebrae, ribs, etc., they are highly suggestive of multiple myeloma and in at least seven instances in this series the correct diagnosis was first suggested by the roentgenologist. Fourthly, there are a certain few cases of multiple myeloma which never exhibit x-ray changes of any type. Two such cases have been seen by us.

From the roentgenographic standpoint the commonest bones involved in order of diminishing frequency were: vertebrae, skull, ribs, pelvis, clavicle, femur, humerus, scapula, fibula, mandible and radius. Any one, or, as is sometimes seen, practically all the bones of the skeleton may be involved.

Rouleaux Formation (60 per cent). Hewson (1777),³⁷ De Senac (1783)³⁸ and Home (1818)³⁹ made note of the phenomenon of rouleaux formation during the process of blood coagulation. In 1851 Wharton Jones⁴⁰ noted the increased tendency to rouleaux formation in persons "labouring under acute rheumatism or inflammation." This fact has been confirmed by many investigators since 1851 but it was not until 1932 that Reimann⁴¹ drew attention to its occurrence in a case of multiple myeloma. The altered plasma proteins so common in multiple myeloma exert a profound effect on many laboratory procedures. Because of excessive rouleaux formation, red blood counts become difficult to do accurately, blood typing may be confusing, the sedimentation rate is extremely rapid and smears of the peripheral blood appear technically imperfect. As Fåhræus⁴² has stated, the phenomenon of excessive rouleaux formation is probably

due to the changes in electric charge which result primarily from the alteration of the albumin-globulin ratio. The exact mechanism of increased rouleaux formation, however, remains obscure. In the last ten cases of myeloma which we have seen, six have shown increased rouleaux formation in the peripheral blood smear. Even in thin areas of the blood smear the red cells are seen to be piled one upon another. Excessive rouleaux formation occurs in other disorders associated with hyperproteinemia and is not distinctive of multiple myeloma. Besides this increased tendency to rouleaux formation there may be a peculiar bright blue coloration of the peripheral blood smear (Wright's stain). This phenomenon has been observed by others¹⁰ and has been attributed to the elevated plasma proteins. We should like to emphasize the importance of these observations which are sometimes of help in the diagnosis of multiple myeloma.

Renal Insufficiency (57 per cent). Urinary function was depressed in thirty-two of fifty-six cases in which phenolsulfonphthalein excretion and urea clearance tests were done. In only one case of Bence Jones proteinuria were these two tests found to be normal. However, this case was later studied more carefully* and by determination of renal blood flow it was found that at least 50 per cent of the renal units were non-functional. Various theories as to how Bence Jones proteinuria interferes with renal function have been postulated. Some authorities believe that there is a "toxic nephritis caused by elaboration of Bence Jones protein." Others have postulated that glomerular damage results from filtration of Bence Jones bodies. Still others have said that damage results from the ischemia caused by large amounts of abnormal protein circulating in the glomerular tuft. Actual tubular obstruction by protein casts associated with degeneration of the renal unit has been considered to be of primary importance. There are many questions to be settled before the true pathogenesis of

* Determinations by Dr. Christine Waterhouse, University of Rochester School of Medicine, Rochester, N. Y.

the renal insufficiency is elucidated. It is interesting that despite the so-called "nephritis" in this condition hypertension is seldom seen (13 per cent). Since Bence Jones proteins are small (35,000–40,000 molecular weight)* and since other proteins which

in twenty-four of forty-five cases (53.3 per cent). Levels of 13 mg. per cent or higher were found in seven of forty-five cases (15.6 per cent). The serum calcium was found to be depressed in four cases and normal in thirty. The average value was 11.0 mg.

TABLE III*
SERUM CALCIUM PHOSPHORUS AND PHOSPHATASES IN VARIOUS BONE DISEASES

Diseases	Calcium	Phosphorus	Acid Phosphatase	Alkaline Phosphatase
Hyperparathyroidism	Elevated	Depressed	Normal	Elevated
Paget's disease	Normal	Normal	Normal	Elevated
Metastatic carcinoma to bones	Elevated infrequently	Normal	Elevated in metastasizing carcinoma of prostate	Elevated
Multiple myeloma	Elevated frequently	Normal	Normal	Slightly elevated

* After Gutman *et al.*¹⁴

are much larger pass through the glomeruli perhaps without doing permanent damage it seems unlikely that the mechanical filtration of this substance alone can be responsible for the renal damage. Blackman¹³ suspects that as the disease progresses and the quantity of urinary Bence Jones protein increases actual tubular obstruction occurs in a certain number of cases and renal failure develops. The true pathogenesis of renal insufficiency in this condition remains a mystery but it is our opinion that once Bence Jones protein is detected in the urine the development of renal insufficiency has begun. As the disease progresses the phenol-sulfonphthalein and urea clearance tests gradually become diminished and finally azotemia develops (the blood non-protein nitrogen was elevated in twenty-six of fifty-seven cases in which determinations were made; 46 per cent). Uremia was the mode of exitus in twelve (43 per cent) of twenty-eight cases in which the terminal condition was clear.

Calcium and Phosphorus Metabolism. The serum calcium and phosphorus in cases of multiple myeloma may be altered. In our laboratory the upper limit of the normal serum calcium level is 11 mg. per cent. Levels higher than this were encountered

per cent. Phosphorus values were elevated (greater than 5 mg. per cent) in cases in which renal failure had developed (ten cases). The alkaline phosphatase activity (Bodansky) was greater than 4.0 Bodansky units in ten cases (48 per cent) of a total of twenty-one cases in which the determination was made. The highest activity was found to be 26.5 Bodansky units and the lowest 1.7 Bodansky units. The average value was 5.2 Bodansky units. The acid phosphatase values (King-Armstrong) in twenty-one cases were all within normal limits. It can be seen from these figures that the following values are usually found in cases of multiple myeloma: (1) normal or elevated serum calcium; (2) normal serum phosphorus (unless renal impairment supervenes in which case the phosphorus level increases); (3) normal acid phosphatase; (4) normal to slightly elevated alkaline phosphatase. The frequent occurrence of the above findings is of distinct aid in the differential diagnosis of hyperparathyroidism, Paget's disease, metastatic carcinoma to bone and multiple myeloma. (Table III.)

The authors do not wish to convey the impression that the determination of serum calcium, inorganic phosphorus and phosphatase activity are diagnostic in cases of multiple myeloma, but rather that these determinations either lend support to or

* Determinations by Dr. Christine Waterhouse, University of Rochester School of Medicine, Rochester, N. Y.

detract from the establishment of such a diagnosis.

Anticomplementary Wassermann (25 per cent). The incidental occurrence of an anticomplementary Wassermann reaction is sometimes the first clue to the discovery of a case of multiple myeloma. This phenomenon is associated with cases in which there is marked hyperproteinemia.

White Blood Count and Peripheral Blood Smear. The white blood count in most of these cases of myeloma was within normal limits (average 8,975 per cu. mm.). Likewise there was little alteration of the differential formula. However, if careful search were made for plasma cells in the peripheral blood, plasma cells were found in small numbers in 25 per cent of the cases in which such a search was made. In two of our cases these cells were present in high percentages, i.e., 62 and 28 per cent. Both cases would have been considered by many to represent cases of plasma cell leukemia. In our opinion, however, there is reason to consider that these two cases represent a variant of the same underlying condition, namely, multiple myeloma.

COURSE

The vast majority of patients in this group pursued a continuous downhill course from the onset of symptoms to the time of death. We have not seen what would be considered a true remission as has been reported elsewhere. Prior to admission to the hospital the average duration of symptoms was nine months. The patient remained in the hospital on the average of forty-three days and the average prognosis from the onset of symptoms was twenty-one months. The longest survival time was five years; the shortest one month.

DIFFERENTIAL DIAGNOSIS

The commonest diseases which were confused with multiple myeloma in this series in order of frequency were: metastatic malignancy to bone, arthritis (rheumatoid, degenerative or infectious), anemia (per-

nicious or iron-deficiency), chronic nephritis, undulant fever, hyperparathyroidism, Paget's disease, ruptured nucleus pulposus, osteomyelitis, leukemia and tuberculosis. Space does not permit a discussion of the differential diagnosis of each of these conditions but it will be seen that the above diseases fall into four main groups: (1) disease of bone; (2) the anemic states; (3) renal disease; (4) certain febrile illnesses. In general, it can be said that the one factor which aided most, either directly or indirectly, in the differential diagnosis of multiple myeloma was the occurrence of abnormalities of the plasma proteins.

The differential diagnosis of disease of the bone is aided materially by a careful study of the serum calcium and inorganic phosphorus levels and a determination of the alkaline and acid phosphatase activity. (Table III.) When this information is added to careful roentgenographic interpretation, much confusion may be averted.

The elucidation of unexplained anemia, whether it be macrocytic, normocytic or microcytic, is aided by the examination of a suitable bone marrow preparation taken from the sternum. Such conditions as pernicious anemia in relapse and iron-deficiency anemia are thereby easily differentiated. As has been stated previously, in only five cases were negative results obtained in a case which later proved to be multiple myeloma.

The differential diagnosis of chronic renal disease is often confusing. However, the frequent occurrence of Bence Jones proteinuria, the low incidence of hypertension and the inability to demonstrate renal disturbance by roentgenographic means all contribute to our ability to distinguish the renal insufficiency of multiple myeloma from other renal disorders.

Various febrile illnesses (undulant fever, tuberculosis, etc.) may be confused with multiple myeloma unless it is realized that fever is a common accompaniment of the latter disease. It is not our intention to give a differential diagnosis of all the febrile illnesses but merely to emphasize that such

illnesses are frequently confused with multiple myeloma.

TREATMENT

Recently Snapper^{45,46,47} has published a series of articles on the effect of stilbamidine and related substances in the treatment of multiple myeloma. No claim is made as to cure of the disease but it has been found that following administration of this drug the patient's pain is frequently alleviated and the roentgenographic spread of the bone lesions is noted to be brought to a temporary halt. We have had limited experience with this type of therapy but such investigation is in progress at the present time at this clinic.

The judicious use of roentgen therapy to relieve the intractable bone pain to which these patients are prone has met with considerable success. It is also interesting to note that the longest survival time (five years) occurred in a patient who received a large amount of x-ray during the course of his disease.

General considerations as to treatment include guarding against too strenuous activity because of the likelihood of pathologic fracture, the maintenance of proper oral hygiene and the judicious use of supportive measures.

CONCLUSIONS

From the experience gained from the study of these cases we conclude that the incidence of plasma cell tumors is greater than had been previously suspected. It is the responsibility of the clinician to recognize the cardinal signs and symptoms of this condition and to request the proper laboratory studies which may corroborate such a diagnosis. It is self-evident that unless the existence of the disease is suspected by the clinician its "accidental" laboratory discovery will be rare indeed. In our present state of knowledge very little of a specific nature can be done for these patients. However, in the interests of making earlier and more accurate diagnoses than in the

past, the following suggestions are made: First, that in any case in which either hyperproteinemia or hyperglobulinemia is discovered, careful electrophoretic studies be carried out. Second, that more attention be paid to the occurrence of rouleaux formation of the red blood cells in the peripheral blood and to the bright blue coloration of the Wright's stained blood smear, and that a satisfactory cause for their presence be found. Third, that any case of unexplained anemia (particularly in the older age groups) be given the benefit of a sternal aspiration and/or sternal biopsy. Fourth, that more energetic and careful searches be made for Bence Jones protein in all urine specimens which contain protein. Fifth, that the level of serum calcium, inorganic phosphorus, alkaline and acid phosphatase be determined in suspicious cases. Sixth, that careful analysis be made of all roentgenographic osteolytic processes and more attention be paid to the occurrence of osteoporosis.

In fifteen cases of myeloma the electrophoretic patterns were similar to those previously reported in this disease. In six cases there was a tall, narrow, abnormal peak migrating more slowly than gamma globulin. This type of pattern had not, to our knowledge, been previously reported. The patterns of these twenty-one cases would in all except one instance justify a presumptive diagnosis of multiple myeloma. Eight cases showed patterns of another type not previously reported. Large abnormal peaks were absent, but there were significant small abnormalities. In six cases of this group the patterns were believed to be strongly suggestive of myeloma. In the two other cases the patterns were only suggestive of some form of malignant disease. In this group of eight cases the incidence of Bence Jones proteinuria was 87.5 per cent. It is suggested that in many cases in which large abnormal peaks are absent, small abnormalities are due to Bence Jones protein in the plasma. The high incidence of Bence Jones proteinuria in this group may result from the absence in the plasma of a

high molecular weight protein capable of forming complexes with Bence Jones protein.

SUMMARY

An analysis of sixty-one cases of plasma cell tumors is given. Particular attention is devoted to the electrophoretic patterns which occur in this condition and suggestions are made which may increase the accuracy and promptness of the diagnosis of this type of tumor. The electrophoretic patterns of twenty-nine consecutive cases of diffuse plasma cell tumor were all abnormal. One case of solitary myeloma of the antrum with low grade chronic infection gave patterns which were normal except for those changes which commonly accompany infection. Five abnormal patterns from cases other than myeloma which might be confused with those of multiple myeloma are shown.

REFERENCES

1. BENGE JONES, H. On a new substance in the urine of a patient with mollities ossium. *Phil. Tr. Roy. Soc. London*, 138: 55, 1848.
2. DALRYMPLE, J. On the microscopical character of mollities ossium. *Dublin Quart. J. M. Sc.*, 2: 85, 1846.
3. MACINTYRE, W. Case of mollities and fragilitas ossium, accompanied with urine strongly charged with animal matter. *Med.-chir. Tr.*, 33: 211, 1850.
4. VON RUSTIZKY, J. Multiples Myelom. *Ztschr. f. Chir.*, 3: 162, 1873.
5. KAHLER, O. Zur Symptomatologie des Multiplen Myeloms: Beobachtung von Albumosurie. *Prague Med. Wchnschr.*, 14: 33, 1889.
6. ELLINGER, A. Das Vorkommen des Bence-Jones'schen Körpers im Harn bei Tumoren des Knochenmarks und seine diagnostische Bedeutung. *Deutsches Arch. f. klin. Med.*, 62: 254, 1889.
7. JACOBSON, V. C. A case of multiple myelomata with chronic nephritis showing Bence Jones protein in urine and blood serum. *J. Urol.* 1: 167, 1917.
8. LONGSWORTH, L. G., SHEDLOVSKY, T. and MAC-INNES, D. A. Electrophoretic patterns of normal and pathological human blood serum and plasma. *J. Exper. Med.*, 70: 399, 1939.
9. SLAVENS, J. J. Multiple myeloma in a child. *Am. J. Dis. Child.*, 47: 821, 1934.
10. BAYRD, E. D. and HECK, F. J. Multiple myeloma—a review of 83 proved cases. *J. A. M. A.*, 133: 147, 1947.
11. WINTROBE, M. M. and BUELL, M. V. Hyperproteinemia associated with multiple myeloma. *Bull. Johns Hopkins Hosp.*, 52: 156, 1933.
12. ATKINSON, F. R. B. Multiple myelomata. *M. Press*, 195: 312, 1937.
13. MAGNUS-LEVY, A. Multiple myeloma. *Ztschr. f. klin. Med.*, 126: 62, 1933.
14. GESCHICKTER, C. F. and COPELAND, M. M. Multiple myeloma. *Arch. Surg.*, 16: 807, 1928.
15. BATTS, M. JR. Multiple myeloma—review of forty cases. *Arch. Surg.*, 39: 807, 1939.
16. GHORMLEY, R. K. and POLLOCK, G. A. Multiple myeloma. *Surg., Gynec. & Obst.*, 69: 648, 1939.
17. COLEY, W. B. Multiple myeloma. *Ann. Surg.*, 93: 77, 1931.
18. MOSCHIKOWITZ, E. Essays on the biology of disease-myeloma. *J. Mt. Sinai Hosp.*, 13: 205, 1946.
19. SVEDBERG, T. and SJÖGREN, B. The molecular weight of Bence Jones protein. *J. Am. Chem. Soc.*, 51: 3594, 1929.
20. SVEDBERG, T. and PEDERSEN, K. O. The Ultracentrifuge. Oxford, 1940. Clarendon Press.
21. MAGNUS-LEVY, A. Über krystallisiertes und amorphes Bence Jones Eiweiss. Multiple myelome. ix. *Ztschr. f. physiol. Chem.*, 243: 173, 1936.
22. BAYNE-JONES, S. and WILSON, D. W. Immunological reactions of Bence Jones proteins. i. Differences between Bence Jones proteins and human serum proteins. *Bull. Johns Hopkins Hosp.*, 33: 37, 1922. ii. Differences between Bence Jones proteins from various sources. *Ibid.*, 119, 1922.
23. HERTOEN, L. and WELKER, W. H. Immunological differences of crystalline Bence Jones proteins. *J. Biochem.*, 34: 487, 1940.
24. MOORE, D. H., KABAT, E. A. and GUTMAN, A. B. Bence Jones proteinemia in multiple myeloma. *J. Clin. Investigation*, 22: 67, 1943.
25. GUTMAN, A. B., MOORE, D. H., GUTMAN, E. B., McCLELLAN, V. and KABAT, E. A. Fractionation of serum proteins in hyperproteinemia with special reference to multiple myeloma. *J. Clin. Investigation*, 20: 765, 1941.
26. SNAPPER, I. Medical Clinics on Bone Diseases. P. 181. New York, 1943. Interscience Publishers, Inc.
27. KERWICK, R. A. The serum proteins in multiple myelomatosis. *Biochem. J.*, 34: 1248, 1940.
28. LONGSWORTH, L. G. Recent advances in the study of proteins by electrophoresis. *Chem. Rev.*, 30: 323, 1942.
29. LONGSWORTH, L. G. A modification of the schlieren method for use in electrophoretic analysis. *J. Am. Chem. Soc.*, 61: 529, 1939.
30. ZELDIS, L. J. and ALLING, E. L. Plasma protein metabolism—electrophoretic studies. Restoration of circulating protein following acute depletion by plasmapheresis. *J. Exper. Med.*, 81: 515, 1945.
31. STERN, K. J. and REINER, M. Electrophoresis in medicine. *Yale J. Biol. & Med.*, 19: 67, 1946.
32. SHAPIRO, S., ROSS, V. and MOORE, D. H. A viscous protein obtained in large amounts from the serum of a patient with multiple myeloma. *J. Clin. Investigation*, 22: 137, 1943.
33. PEDERSEN, K. O. Ultracentrifugal studies on serum and serum fractions. Almqvist and Wiksells Boktryckeri, A. B. Uppsala.
34. MARTIN, N. H. A study of the plasma and tissue globulins in myelomatosis. Program Thirty-ninth Annual Meet., Am. Soc. Clin. Investigation, p. 23. May 5, 1947.

35. WINTROBE, M. M. *Clinical Hematology*. Philadelphia, 1946. Lea and Febiger.
36. FAIRMAN, E. and WHIPPLE, G. H. Bone marrow volume in adult dogs. *Am. J. Physiol.*, 104: 352, 1933.
37. HEWSON. *Experimental enquiries*. 3: 28, 1777.
38. DESENAC. *Traité de la Structure du Cœur* Livre. 2nd ed., p. 5, 1783.
39. HOME, E. On the changes the blood undergoes in the act of coagulation. *Phil. Tr. London*, 108: 176, 1818.
40. WHARTON-JONES, T. On the state of the blood and the blood vessels in inflammation. *Guy's Hosp. Rep.*, 7: 1, 1851.
41. REIMANN, H. A. Hyperproteinemia as a cause of autohemagglutination. *J. A. M. A.*, 99: 1411, 1932.
42. FÅHREUS, R. The suspension stability of the blood. *Acta med. Scandinav.*, 55: 1, 1921
43. BLACKMAN, S. S., JR., BARKER, W. H., BUELL, M. V. and DAVIS, B. D. On the pathogenesis of renal failure associated with multiple myeloma. Electrophoretic and chemical analysis of protein in urine and blood serum. *J. Clin. Investigation*, 23: 163, 1944.
44. GUTMAN, A. B., TYSON, T. L. and GUTMAN, E. B. Serum calcium, inorganic phosphorus, and phosphatase activity in hyperparathyroidism, Paget's disease, multiple myeloma and neoplastic disease of bones. *Arch. Int. Med.*, 57: 379, 1936.
45. SNAPPER, I. On the influence of stilbamidine upon multiple myeloma. *J. Mt. Sinai Hosp.*, 13: 119, 1946.
46. SNAPPER, I. and SCHNEID, B. On the influence of stilbamidine upon myeloma cells. *Blood*, 1: 534, 1946.
47. SNAPPER, I. Stilbamidine and pentamidine in multiple myeloma. *J. A. M. A.*, 133: 157, 1947.

Test for the Presence of the "Hypertensive Diencephalic Syndrome" Using Histamine*

HENRY A. SCHROEDER, M.D. and MELVIN L. GOLDMAN, M.D.†

St. Louis, Missouri

PAGE has described a syndrome associated with arterial hypertension which he called the "hypertensive diencephalic syndrome."¹ We quote from his description: "This syndrome was described as occurring usually in young and middle-aged women, though it may be seen occasionally in men. It is characterized by hypertension of the labile sort, more especially by the periodic appearance of a blotchy blush which extends down over the face and upper chest, seldom, if ever, involving the limbs. Indeed, the extremities may be cold, pale or have a dusky, mottled hue during an attack. Over the area of blush are minute beads of perspiration. Lacrimation or merely "watering" of the eyes may occur without an associated emotional counterpart. Tachycardia and hyperperistalsis are common. These episodes occur without apparent cause or may be brought on by embarrassment and excitement."²

Penfield³ first described a syndrome similar to this which occurred in a patient with a tumor of the third ventricle; he called it "diencephalic autonomic epilepsy." Symptoms and signs can be grouped roughly as disturbances of function of three components of the autonomic centers: (1) Emotional instability can be seen by the excessive nervous tension and anxiety from which these patients suffer from time to time as well as attacks of uncontrollable and unreasonable weeping. These latter appear to bear no relation to the patient's inner emotional status at the time of the

attack; she is unable to give a reason for her actions which come on spontaneously at any time and which are senseless to her. Many of the less severely disturbed patients do not exhibit these outbursts but may complain of attacks of emotional tension appearing without reason. (2) Vasomotor instability is shown by lability of the blood pressure (even after many years of sustained hypertension), the characteristic blotchy blush on the skin and recurrent episodes of cold, clammy and pale or cyanotic extremities. Blood pressure is usually higher when the blush is present. (3) Autonomic instability is evidenced by excessive perspiration, attacks of emotional polyuria, deep sighing respirations (often seen on the tracing made for determination of the basal metabolic rate) and the occasional presence of low grade fever. Often the patients' only complaints are of attacks of the nature described. Sometimes the headaches from which they suffer occur only during such attacks. We have noticed the presence of this syndrome in certain hypertensive patients for a number of years⁴ and have believed with Page that it represented a neurogenic component which could be differentiated from other pathogenic factors.

The curious blotchy rash or blush is the most common characteristic of this syndrome. (Figs. 1 to 3.) We have seen it over the chest and back, upon arms, neck and face but rarely on the abdomen. In women it usually does not appear in the area over the shoulders subject to chronic compression by straps of clothing. Occasionally areas on

* From the Department of Internal Medicine and the Oscar Johnson Institute, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo., under a grant-in-aid from the U. S. Public Health Service, National Institutes of Health.

† National Institutes of Health Postdoctorate Research Fellow.

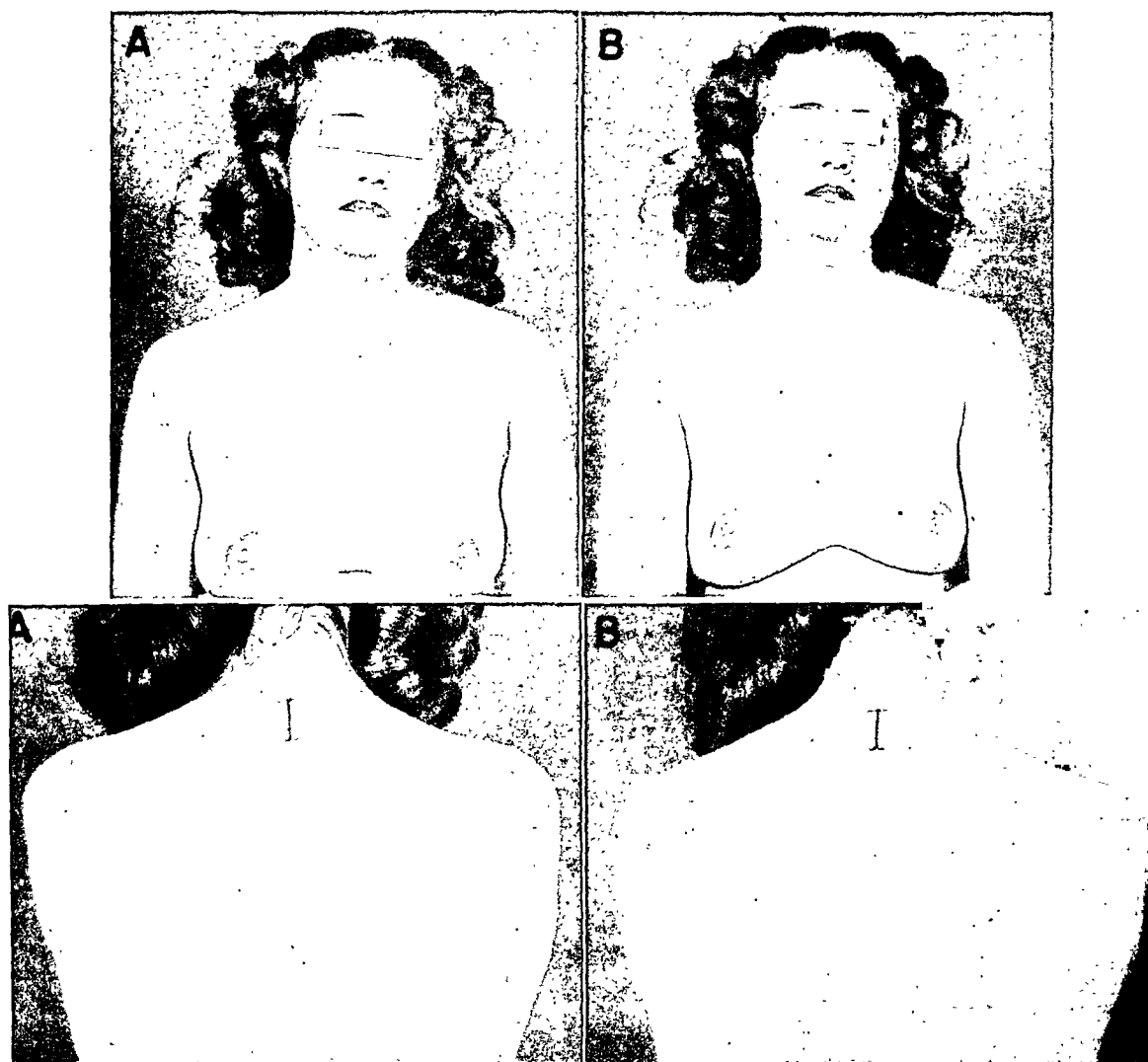


FIG. 1. Blotchy blush appearing ten minutes after the intradermal injection of 0.25 mg. of histamine into the left forearm of a twenty-eight year old woman; A, before B, after injection. Note the rash on the upper arms, neck, back and shoulders; circumoral pallor can be seen faintly; the rash was a bright red. Hypertension was of the labile type. Although this reaction was repeatedly demonstrated, it disappeared after lumbodorsal sympathectomy.

the face are brilliant red or purplish with a sharp line of demarcation next to one which is dead white.

Because this syndrome is common, interesting speculatively and suggests certain manifestations of a discharge of impulses from the hypothalamus through the autonomic nervous system and because it has been reproduced by stimulation of the hypothalamus, a test to bring it out is of some value for studying it further. If these manifestations, dramatic as they are, are concerned with some specific underlying mechanism of certain types of hypertension, such a test might be used to differentiate cases of one variety from another.

Accordingly, attempts were made to reproduce the attacks by a method other than induction of embarrassment or excitement. It was soon found in many cases that histamine injected intradermally would cause the blush and other characteristic symptoms to appear. Therefore, this test was applied to a number of patients, some with normal blood pressures and some with hypertension

METHOD

With the patient recumbent, 0.25 cc. of histamine acid phosphate solution (0.25 mg. of histamine base) was injected intradermally into the volar surface of the forearm. As this amount of fluid was fairly large

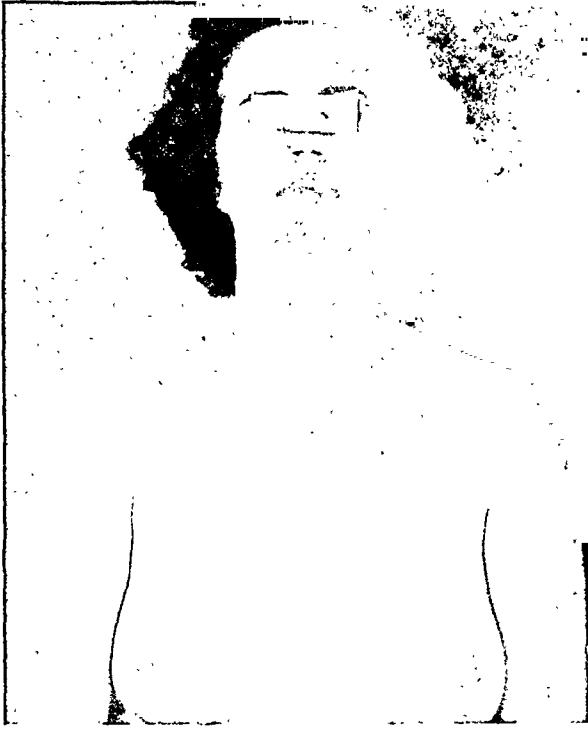


FIG. 2. Blotchy erythema resulting from the intradermal injection of histamine in a thirty-two year old woman exhibiting "neurogenic" hypertension. Note areas on the shoulders where straps from underclothing had compressed the skin.

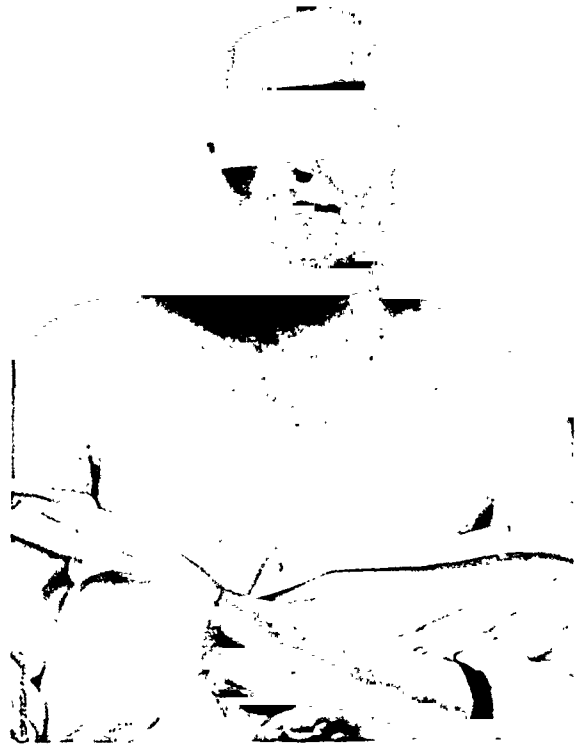


FIG. 3. Typical diencephalic blush induced by emotion in a thirty-seven year old woman who had suffered from a severe but labile hypertension for fifteen years.

some of the material probably escaped into subcutaneous tissues. The injection was accompanied by a sharp, severe pain not unlike that of a bee sting which subsided rapidly. Five, ten and fifteen minutes later patients were examined carefully for skin manifestations and were questioned closely for symptoms. Any complaint similar to those usually experienced (headache, palpitation, etc.) was especially noted. Blood pressure changes were recorded in many by the auscultatory method.

One hundred three ward and clinic patients were so tested, fifty-three of whom suffered from arterial hypertension and fifty did not. There was some tendency to test more patients exhibiting clinical signs of "neurogenic" hypertension because it was soon found that these were the type giving positive responses. Of the hypertensives, sixteen were males and thirty-seven were females; there were twenty-five normotensive males and twenty-five females. An attempt was made to classify

them according to a plan previously described.⁴

No attempt was made to control the temperature of the room in which the test was made but it was never excessively cold. No effect of outside temperature or weather was seen in the results.

The following criteria were graded 1 plus to 4 plus: (1) Flushing of the face and circumoral pallor which were present to some degree in most cases and were recorded but not considered in the overall evaluation of the test. (2) Headache; the type, location, severity and duration of which were recorded and graded. Special attention was paid to the resemblance of the headache produced by histamine to that typically experienced as a result of hypertension. (3) Tearing or lacrimation; mere watering of the eyes to uncontrollable outbursts of weeping and sobbing were graded and attention was given to the presence of similar attacks in the history of the patient.

(4) Blotchy erythema; the presence and degree of the mottled blush on the face, back, neckline, chest and abdomen was noted. The presence of a "strap line" of normal skin on the shoulders where compression from undergarments had occurred was recorded. (5) Local reaction; the presence of a wheal and erythema at the site of injection was noted. (6) The total reaction, based upon an evaluation of the aforementioned signs, was graded as negative or 1 plus to 4 plus. The blush was given greatest weight in this estimation.

RESULTS

Sixteen hypertensive patients showed a reaction to histamine considered as 3 or 4 plus. (Table 1.) Of these, all were considered to exhibit clinical signs of "neurogenic" hypertension in that blood pressures were labile, vascular disease was minimal, the course was usually benign and there were associated emotional disturbances. Sixteen more patients of a similar type gave a reaction considered as 2 plus, a definite although less marked response. Only seven of this type did not react or reacted only slightly. In addition four patients exhibiting associated disturbances suspected to be of endocrine origin, two suffering from general arteriosclerosis and seven of eight classified in an "unknown" category gave negative to minimal reactions. Only one patient in this group showed a 2 plus reaction. The blush and other symptoms appeared three to five minutes after injection and reached its greatest intensity in ten minutes. It usually lasted fifteen to thirty minutes, fading gradually.

Two patients exhibiting occasional slight elevations of blood pressure were considered to be "prehypertensive." In one patient a marked reaction was elicited and in the other a mild reaction was seen.

Of the normal controls forty patients did not react in this manner to histamine, five reacted slightly and only five showed responses considered 2 to 4 plus. Two of these suffered from psychoneurosis and low grade fever of unknown origin, one of Hodgkins

disease, and one of mild rheumatoid arthritis with slight elevation of systolic blood pressure, cold moist extremities and palpitation.

Tests were repeated weeks or months apart in six patients who reacted and similar

TABLE 1
RESULTS OF "HISTAMINE TEST" IN ELICITING SIGNS AND SYMPTOMS OF HYPERTENSIVE DIENCEPHALIC SYNDROME

	Reaction					Total	Total Positive*	
	0	+	++	+++	++++		No	Per Cent
Normotensive subjects:								
Male.....	22	1	1	1	0	25	2	8
Female.....	18	4	0	1	2	25	3	12
Hypertensive subjects:								
Neurogenic type								
Male.....	1	2	7	2	2	14	11	79
Female.....	2	2	9	4	8	25	21	84
Other types:								
Male.....	2	0	0	0	0	2	0	
Female.....	8	3	1	0	0	12	1	8

* Positive includes reactors of ++ or greater.

results were obtained. Three female patients who repeatedly had reacted excessively to the drug were subjected to lumbodorsal sympathectomy; excellent early results were obtained and their blood pressures remained at normal levels. Post-operatively none of them reacted to histamine. A markedly positive response in another disappeared after operation although blood pressure did not fall to normal levels.

Attempts were made to block this reaction in one by the use of antihistaminic agents but were unsuccessful although the blush produced was of somewhat less intensity. Epinephrine (0.5 mg.) given subcutaneously in four did not reproduce the train of events nor did acetyl- β -methyl choline chloride (12.5 mg.) or yeast adenylic acid (10 mg.).

Headache typical of that usually experienced was reproduced in fourteen hypertensive subjects by histamine. The remainder did not complain of headaches during the test. In thirteen normotensive individuals headache was initiated; in four

it was severe and similar to that previously experienced. One of these was found to have a chromophobe adenoma of the pituitary.

Attacks simulating presenting symptoms were initiated by histamine in most of those patients in whom the test was positive. Aside from the blush and headache, symptoms included: severe spells of weeping (3 patients), dizziness (6 patients), palpitation (10 patients), excitement and anxiety (2 patients) and tachycardia (4 patients). In no patient was generalized vascular collapse produced.

In two hypertensive subjects intradermal histamine produced symptoms of severe headache, palpitation, tachycardia and elevation of blood pressure similar to those seen in cases of pheochromocytoma after its intravenous use.³ No blush appeared in these individuals. Opportunity for further study on one patient was not given; the other showed a moderate response to the Roth-Kvale test but exploration failed to reveal a tumor in the adrenal gland.

COMMENTS

The mechanism by which intradermal histamine reproduces attacks of the "hypertensive diencephalic syndrome" is not known. One can speculate that histamine directly stimulates certain elements of the autonomic nervous system, stimulates the same elements indirectly by eliciting some other mediator (for example epinephrine or sympathin), or acts directly on skin, nerve tissue and blood vessels. Since epinephrine itself did not produce these symptoms it is unlikely that the mechanism is the same as that suggested by Roth and Kvale for patients with pheochromocytoma.⁵ Reproduction of the typical hypertensive headache in a certain proportion of cases suggests that histamine may be concerned in some manner with these headaches, as well as with other symptoms of which these patients complain.

Whether incomplete metabolism of histidine is present in some cases of arterial hypertension is not known but might be

suspected by analogy from the work of Holtz.⁶ However, we have not seen a positive histamine test in patients with severe renal impairment secondary to hypertension.

This test has been of some value in estimating the degree and presence of the "neurogenic" element in cases of arterial hypertension. Strongly positive reactions were seen only in this type. While the series is small, the results suggest that some such test as this may be of aid in differentiating certain types of individuals from others. Whether it will be of value in the selection of patients for sympathectomy remains to be proven; in a small series operated upon in this hospital, three of the best immediate results were in patients reacting strongly to this test.

Like all such procedures the results are not clear-cut, and the criteria for their evaluation inexact. But from a superficial analysis one can assume that if patients react strongly to histamine in the manner described, they are likely to have a fluctuating blood pressure, a relatively benign course, relatively little renal disease, attacks similar to that produced by the test, and general vascular and emotional lability.

SUMMARY

A test using the intradermal injection of 0.25 mg. of histamine has been described which appears to reproduce attacks typical of the "hypertensive diencephalic syndrome." It also reproduces in some hypertensive patients other symptoms of which they complain. Few normotensive patients respond to histamine in this manner. It is suggested, therefore, that histamine-like substances may be concerned in the causation of some of the symptoms common to many hypertensive patients, especially those exhibiting the "neurogenic" type.

Acknowledgment. The authors are indebted to Dr. Palmer H. Fitcher and Dr. John A. Nuetzel for performing some of the tests. Photographs in Figs. 1 and 2 were made by Mr. K. Cramer Lewis of the Department of Illustration, Washington University School of Medicine, and

in Fig. 3 by Mr. Joseph B. Haulenbeek of the Rockefeller Institute.

REFERENCES

1. PAGE, I. H. A syndrome simulating diencephalic stimulation occurring in patients with essential hypertension. *Am. J. M. Sc.*, 190: 9, 1935.
2. PAGE, I. H. and CORCORAN, A. C. Arterial Hypertension, Its Diagnosis and Treatment. Chicago, 1946. The Year Book Publishers.
3. PENFIELD, W. Diencephalic autonomic epilepsy. *Arch. Neurol. & Psychiat.*, 22: 358, 1929.
4. SCHROEDER, H. A. and STEELE, J. M. Studies on "essential" hypertension. I. Classification. *Arch. Int. Med.*, 64: 927, 1939.
5. ROTH, G. M. and KVALE, W. F. Tentative test for diagnosis of pheochromocytoma. *J. Lab. & Clin. Med.*, 30: 366, 1945.
6. HOLTZ, P., CREDNER, K. and WALTER, H. Über die Spezifität der Aminosäuredecarboxylasen. *Ztschr. f. physiol. Chem.*, 262: 111, 1939.

Treatment of Thromboangiitis Obliterans

Two-year Follow-up after Sympathectomy

WILLIAM J. MESSINGER, M.D.,* EDMUND N. GOODMAN, M.D.*

New York

and JAMES C. WHITE, M.D.†

Boston, Massachusetts

IN a previous report Goodman, Messinger and White¹ reported their experiences with patients favorably influenced by intervention on the autonomic nervous system. The immediate results achieved in thromboangiitis obliterans were so impressive that it was decided to sympathectomize all new proven cases in which high vasoconstrictor tone could be demonstrated and to subject these individuals to periodic review in order to gauge the long term effectiveness of treatment. This report is concerned with an evaluation of nineteen patients with thromboangiitis obliterans treated by sympathectomy.

METHODS OF STUDY

These were as described in our previous report,¹ with the following additions: A psychiatrist was invited to participate in the evaluation of patients. Photographs of the involved extremities of all patients were obtained in color prior to and following sympathectomy as objective records. Since blocking of the paravertebral ganglia by means of procaine taxes the patient, personnel and facilities, tetraethyl ammonium chloride,‡ a drug which blocks the autonomic ganglia, in the dosage of 7 to 10 mg. per Kg. intravenously was employed and proved to be an acceptable substitute. The pharmacologic properties of this drug have been the subject of previous reports by Lyons et al.² The side-effects of the drug sometimes incapacitated a patient temporarily, rendering him unfit for immediate ambulation.

When the effect of sympathectomy on the

patients' claudication time was investigated, procaine block of the paravertebral sympathetic ganglia was again the procedure used. In an attempt to obtain evidence of increased deep blood flow of the extremities following sympathectomy we recently have been subjecting all new patients before and after operation to the ergometric procedure reported by Hitzrot et al.³ These results will be the subject of a future report. Finally, to evaluate properly some individuals with vague extremity pain we found the technic of Naide⁴ to be most useful in excluding bizarre vascular manifestations of early arthritis. Patients with massive gangrene or infection were treated initially in the manner described in our previous report.

Surgical Technic. For lumbar sympathectomy the patient is placed in a lateral position with knees bent and hips flexed. A hockey-stick-type incision is used, extending from the border of the semispinalis muscle at the level of the twelfth rib to a point 2.5 cm. above the anterior superior spine of the ilium. A portion of the external oblique muscle is cut, the transversalis fascia split and the lumbodorsal fascia incised. The retroperitoneal space is thus exposed and the abdominal contents are stripped forward simply by hugging the quadratus lumborum and psoas muscles. The sympathetic chain can now be visualized at the junction of the psoas muscle and vertebral body. Due caution must be exercised to prevent injury to the ureter and the vena cava on the left and aorta and ureter on the right. With the aid of a long nerve hook, the sympathetic chain is held and the individual rami of the ganglia to be removed are clipped with silver brain clips and the chain proximal and distal to the ganglia doubly clipped prior

*Now on the Vascular and The Neurosurgical Services, U.S.N.H., St Albans, N. Y.

†Now on the Neurosurgical Service, Massachusetts General Hospital, Boston, Mass.

‡Etamon, generously supplied by Parke, Davis & Co.

to resection of the ganglia. Silk closure is used with all spaces closed tightly and air-free.

A prerequisite for thoracic sympathectomy is intratracheal anesthesia. The patient is placed in a prone position with a pillow under his chest to accentuate the upper thoracic spinal curve while the arms are allowed to fall free in order to throw the scapulae anteriorly. At the level of T₁ an 8 cm. incision is made, extending to the level of T₄, 4 cm. lateral to the spinous processes. A 4 cm. section of the third rib is removed from its vertebral attachment. The endothoracic fascia can now be incised, pleura and lung retracted from the rib surfaces and the area from first to fourth rib exposed. The second and third intercostal nerves are identified and their communicating rami with the sympathetic chain are divided. By exerting gentle traction on the intercostal nerves the anterior and posterior roots are brought into view and the nerves severed at their emergence from the intervertebral foramina. The sympathetic chain, held with a nerve hook, is divided below the fourth ganglia and the length of the chain, including the second, third and fourth ganglia, is covered with tantalum foil so that the distal end is capped and bent on itself. The chain is then anchored into the semispinalis muscle in a cephalad direction. The use of the foil in this manner and the diversion of the chain in the cephalad direction are emphasized since we believe the maneuver effectively prevents regeneration in most instances.

Distribution of Cases. All of our patients were males, all were smokers. Significantly, they indicated a one- to threefold increase in smoking either upon entrance into service or since release from service. The colored race was not represented, but no special racial distribution was apparent. The youngest patient was twenty years and the oldest fifty-four years of age. The symptoms and findings of each patient are recorded briefly in Table 1. The presence of Raynaud's syndrome, of migratory phlebitis and of involvement of all four extremities in this group approximates the incidence reported in a larger series of cases by Freeman⁵ from the Army Vascular Centers. The presence of epidermophytosis in some of these patients may have been contributory to their phlebitis. It is more likely that the increased growth of the fungus was due to hyperhidrosis and the vein involvement a primary manifestation of the underlying vascular dis-

ease. It should be noted that all of our patients were either Navy personnel or veterans of the services.

RESULTS

No patient's symptoms were worse after operation and no fatalities occurred due to operation. Pain in all patients subjected to operation was relieved within forty-eight hours after the procedure was carried out so that the use of narcotics and analgesics could be discontinued as soon as discomfort from the operative site ceased. Reversal of color changes started immediately after operation and ulcerated gangrenous areas generally began to heal promptly. In a few patients color changes and symptoms became worse five to seven days following operation. This was of short duration and thought to be due to the transient burst of vasoconstrictor and sudomotor activity that generally occurs at this time after any peripheral sympathetic denervation. This phenomenon had been previously described by White and Smithwick.⁶ There were no amputations in this series. No patient was bedridden more than four days because of the operative procedure. All patients except one (Case xviii) reported significant amelioration of claudication (when present) within a week after operation and progressive improvement thereafter. In this connection it is only fair to state that in those with longstanding symptoms and muscle wasting, complete rehabilitation was naturally of longer duration. It is true nevertheless that the majority of our patients were able to return to work in four to six weeks without recourse to further medical treatment. Signs of nerve regeneration have not appeared in this group.

Since the preservation of sexual function in the age groups found in this series was of some concern to the patients, the first lumbar ganglion was spared whenever possible. As our experience accumulated it became apparent that the first lumbar ganglia were not of prime importance for the preservation of erection and ejaculation. This observation was significant because

these ganglia control the important area from knee to hip. To summarize our observations concerning sexual disturbances resulting from lumbar sympathectomy in over one hundred cases we can state the following: No patient reported permanent disturbance of erection or ejaculation as a result of unilateral operation when L₁ was included in the ganglia removed. Practically all patients reported disturbances after bilateral operation. These consisted of failure of erection, loss of ejaculation or both although L₁ was excluded in some instances. Between these extremes various complaints were noted, none of which appeared to incapacitate the individual's sexual powers permanently. We therefore can conclude from our observations that no single lumbar ganglion controls the sexual functions and that these functions most likely are mediated bilaterally through the lumbar ganglia. Unfortunately, we have no reliable data with regard to sterility in these individuals after operation.

COMMENTS

Silbert,⁷ who has followed more than 500 individuals with this disease from two to fifteen years, has indicated that cessation of smoking will cause the disease to be self-limiting, and in some early cases this alone appears to be sufficient to result in relief of symptoms. We believe that there is general agreement with this statement. It should also be self-evident from the reports on the multiplicity of medicinal, thermal and mechanical agents used in the treatment of this disease that the patient requires further therapy after he gives up use of tobacco.

In the light of newer knowledge concerning peripheral blood flow, re-examination of the evidence forming the basis for some of the medicinal treatments in thromboangiitis obliterans appears to be in order. For example, Friedlander et al.,⁸ using muscle and skin thermocouples, reported that after such procedures as reflex body heating, block of the sympathetic ganglia

by procaine and spinal anesthesia, skin temperature increased while muscle temperature remained unchanged. Intravenous injection of 300 cc. of 5 per cent sodium chloride caused both increase in muscle and skin temperature. That muscle temperature changes can be used as an index of muscle blood flow has been challenged by Wilkins⁹ and most recently by Barcroft and Edholm.¹⁰ These investigators oppose such inferences since muscle is so much less vascular than skin that the release of vasoconstrictor tone causes far less increase in blood per unit volume of tissue than it does in skin. In addition they emphasize the fact that unless every precaution is taken to prevent cooling of the limb prior to sympathetic block the muscle blood flow would be subnormal and the effect of the block reduced.

All our patients with thromboangiitis obliterans were found to be inveterate smokers. This situation prevailed despite the fact that they had been persistently warned against smoking. It was gratifying to note in eleven of our patients apparent reversal of this attitude after sympathectomy. We do not doubt that some will again return to the habit, not because of recurrence of symptoms but mainly because of the social amenities and modern advertising practices. This seems to be confirmed in our follow-up. (Table 1.)

Surgical interruption of sympathetic pathways for thromboangiitis obliterans does not originate with us. Harris,¹¹ Freeman and Montgomery,¹² Leriche¹³ and deTakats¹⁴ are among those whose reports indicate that the procedure has a favorable influence on the course of this disease. In a report summarizing the Army's wartime experience in its vascular disease centers, Freeman⁵ states that 53 of 160 patients with thromboangiitis obliterans were treated by sympathectomy. Of these three failed to improve and these were patients who continued to smoke. In this connection a brief review of the history of Case xviii is interesting since this patient failed to maintain his

TABLE I
TREATMENT OF THROMBOANGIITIS OBLITERANS WITH SYMPATHECTOMY

Case No.	Name	Age	Symptoms	Duration	Pertinent Findings	Operation	Two-year Follow-up
I	S. B.	22	Calf and foot pain bilaterally upon walking, relieved by rest	?	Absent pedal pulses; diminished calf oscillometric readings; cool hyperhidrotic feet; marked blanching on elevation; marked delay in vein filling in dependency	Bilateral lumbar sympathectomy, L ₂ , L ₃	Warm, dry feet immediately after operation; asymptomatic and not smoking
II	P. C.	23	Raynaud's syndrome of both lower extremities with hyperhidrosis; severe calf pain on walking, also Raynaud's syndrome of upper extremities	2 yr.	Pallor and numbness of feet on elevation and rubor on dependency; diminished post-tibial and dorsalis pedis pulsations; pallor of both hands on elevation and rubor on dependency; diminished right radial pulsation and poor ulnar collaterals on left	Bilateral lumbar sympathectomy, L ₂ , L ₃ ; bilateral thoracic sympathectomy, T ₂ , T ₃ , T ₄ and second intercostal nerve rhizotomy	Immediate reversal of color changes in all extremities after operation; occasional pain in legs in cold weather; unlimited exercise tolerance. Dorsalis pedis pulses remain diminished but left ulnar collateral circulation is good; smoking
III	C. D.	24	Numbness, pain and coldness of fingers and toes; ulceration of fingertips of 3 months' duration	5 mo.	Marked hyperhidrosis of hands and feet with severe color changes upon change in position; ulceration of all fingertips; all major pulse diminished in the upper and lower extremities, left posterior tibial and both dorsal pedis pulses absent	Bilateral lumbar sympathectomy, L ₂ , L ₃ ; bilateral thoracic sympathectomy, T ₂ , T ₃ , and second intercostal nerve rhizotomy	Prompt healing of finger ulcerations after operation and reversal of color changes; good exercise tolerance; no increase in major pulsations; not smoking
IV	M. D.	24	Claudication walking 2 blocks; necrotic ulcer, paronychia 4th left toe	3 mo.	Cold sweaty feet with cyanosis on dependency, blanching on elevation; absence of dorsalis pedis and post-tibials bilaterally, and right popliteal; oscillometric readings diminished in right calf and both feet	Bilateral lumbar sympathectomy, L ₂ , L ₃	Prompt healing of ulcer with early loss of claudication; not smoking; asymptomatic; major pulsations have not returned; no color changes
V	D. E.	45	Numbness of feet; aching of legs and feet on walking; discoloration of feet while dependent, left worse than right	17 yr.	Cold cyanotic feet with diminished skin temperature; all pulses except femorals absent; femoral pulses diminished; no calcification of arteries in legs by x-rays; biopsy of left posterior tibial artery reported as pathognomonic of thromboangiitis obliterans	Transabdominal sympathectomy, L ₂ , L ₃ , L ₄	Has required no further medical attention; feet are warm and dry and of good color; progressive exercise tolerance without claudication; not smoking

TABLE I (Continued)

Case No.	Name	Age	Symptoms	Duration	Pertinent Findings	Operation	Two-year Follow-up
VI	C. F.	36	Swelling, redness and pain in both feet; claudication upon walking 2 blocks	3 yr.	Marked color change and coldness of lower extremities; absence of all pulsations, except the femorals which were diminished; both radial pulses diminished and ulnar collateral circulation poor	Bilateral lumbar sympathectomy, L ₁ , L ₂ , L ₃ , L ₄	Progressive relief of claudication and reversal of color changes in lower extremities; feet are warm, dry and painless; both hands are cool and hyperhidrotic; there is beginning ulceration of the tip of the 5th finger, left hand; patient requests thoracic sympathectomy; smoking
VII	H. F.	43	Pain and discoloration of feet; claudication of left calf; one episode of Raynaud's syndrome involving 4th and 5th fingers, left hand	Left leg, 5 yr.; right leg, 3 yr.	Both feet are blue, cold, and hyperhidrotic; changes are more severe in the left foot; only femoral pulses palpable; chronic area of dermatitis present on left ankle	Left lumbar sympathectomy, L ₂ , L ₃	Patient ceased smoking immediately after operation; progressive loss in claudication noted; color changes in left foot became minimal; after 3 weeks the foot became warm and dry; color changes in right foot became minimal in 4 months but the foot remained cool and hyperhidrotic; returned 2 years after operation because of thrombophlebitis of right calf directly related to resumption of smoking; left foot warm and asymptomatic; working up to time of thrombophlebitis
VIII	S. J.	20	Pain and swelling of left foot	?	Absent pedal pulses and left posterior tibial; ulcerations of left 4th and 5th toes; both feet cold and cyanotic; marked pallor on elevation of feet with slow return of color on dependency	Left lumbar sympathectomy L ₂ , L ₃	Immediate warming of left foot with loss of pain after operation; prompt healing of ulcerations; right foot is cool and moist now but left is warm and dry; no color changes in either; asymptomatic; not smoking
IX	R. K.	45	Increasing claudication, left calf; cold, wet left foot	1 yr.	Left calf 3.5 cm. less in diameter than right both dorsalis pedis, left posterior tibial and left popliteal pulsations absent; cool feet with marked rubor and tenderness of first toe, left foot	Left lumbar sympathectomy, L ₁ , L ₂ , L ₃	Marked relief of symptoms immediately after operation; reversal of color changes in left foot; claudication has progressively decreased so that he can play golf without symptoms; not smoking

TABLE I (Continued)

Case No.	Name	Age	Symptoms	Duration	Pertinent Findings	Operation	Two-year Follow-up
x	A. L.	43	Right hand cold and hyperhidrotic; marked blanching and rubor	6 mo.	Necrotic ulcerations of the fingertips 2-5, right hand; right ulnar pulse absent, radial diminished; marked hyperhidrosis of right hand	Right thoracic sympathectomy, T ₂ , T ₃ and 2nd intercostal nerve rhizotomy	Right hand warm and dry; no change in pulsations; ulcerations healed promptly after operation; left hand hyperhidrotic and left ulnar pulse absent; Raynaud's phenomena of left hand; both post-tibial pulses very faint but denies leg symptoms; requests left thoracic sympathectomy; smoking
xi	J. L.	36	Painful, cold, discolored fingers right hand; painful right leg with 2 block calf claudication	14 mo.	Evidence of migrating phlebitis in lower extremities; cold, tender ulcerated right 4th and 5th fingers with color changes; marked tenderness over right ulnar artery; decreased oscillometric readings on left forearm; moderate rubor of both feet; absent dorsalis pedis and posterior tibial pulses	Bilateral lumbar sympathectomy, L ₁ , L ₂ ; bilateral thoracic sympathectomy, T ₂ , T ₃ , T ₄ and 2nd intercostal nerve rhizotomies	Immediate relief of pain in hands after operation; rapid loss of claudication and healing of finger ulcers; gradual reversal of color changes; rarely smokes and is asymptomatic
xii	E. M.	43	One half block claudication of both legs; numbness and tingling of the hands with episodes of Raynaud's syndrome of 1st, 2nd and 3rd fingers	6 mo.	Marked dermatophytosis of feet and hyperhidrosis of hands and feet; left radial pulse absent and 2nd and 3rd fingers cold and blue; both posterior tibial arteries barely palpable; no calcification of extremity vessels noted by x-ray	Bilateral thoracic sympathectomy, T ₂ , T ₃ and 2nd intercostal nerve rhizotomies; bilateral lumbar sympathectomy, L ₁ , L ₂	Immediate relief of hand symptoms; can walk 1 mile in cold weather without claudication; coldness of 2nd and 3rd fingers, left hand which persists but color is good; posterior tibial pulsations are improved and confirmed by oscillometric readings. Smoking
xiii	P. O'C.	36	Bilateral claudication with coolness and discoloration of the feet; one episode of Raynaud's syndrome right hand; 2 episodes of phlebitis, left leg	18 mo.	Marked color changes and hyperhidrosis of both feet; only femoral pulses palpable; marked delay in vein filling	Bilateral lumbar sympathectomy, L ₁ , L ₂	Dry, warm, lower extremities immediately after operation; rapid reversal of color changes with nearly normal vein filling; major pulses have not returned; gradual diminution in claudication; not smoking
xiv	J. R.	38	Pain and ulceration of 1st toe, right foot	7 mo.	Right foot violaceous in color with a necrotic ulcer extending into the base of the 1st joint; both dorsalis pedis pulses absent in addition to the right posterior tibial	Right lumbar sympathectomy, L ₁ -L ₄ ; disarticulation of terminal phalanx	Immediate results were good; now has bilateral claudication, worse in left calf, right foot is warm with better vein filling than left; denies smoking

TABLE I (Continued)

Case No.	Name	Age	Symptoms	Duration	Pertinent Findings	Operation	Two-year Follow-up
xv	L. R.	33	Said to have had trench foot in 1944; pain, swelling, redness and coldness of the 1st and 2nd toes of left foot	2 wk.	Swelling and rubor of left foot; left foot cold, right cool; draining ulcerations present on tips of 1st and 2nd toes, left foot; left dorsalis pedis and posterior tibial pulses absent; left foot markedly hyperhidrotic; no stigmas of trench foot found	Left lumbar sympathectomy, L ₁ , L ₂	Toe ulcers had healed within 3 wk. after operation; feet are warm, dry and pink with minimal blanching of left foot on elevation; left posterior tibial artery faintly palpable; rarely smokes now
xvi	H. W.	33	Cyanosis, swelling and tenderness of left foot	1½ yr.	Cyanotic, cold left foot; dorsalis pedis pulses absent bilaterally; absent left posterior tibial pulse; severe blanching of left foot on elevation with slow return of color on dependency	Left lumbar sympathectomy, L ₁ , L ₂ , L ₃	Warm, painless foot immediately after operation; asymptomatic; posterior tibial pulse is palpable; unlimited exercise tolerance; not smoking
xvii	L. W.	54	Claudication, both legs and feet; ulceration of 3rd toe right foot of 1 week's duration; original diagnosis of thromboangiitis obliterans of left lower extremity made at Mt. Sinai Hospital more than 20 yr. ago; original history includes migratory phlebitis and Raynaud's syndrome of lower extremities; insists he has not smoked in 20 yr.	29 yr.	All pulses except femorals absent in lower extremities; right femoral pulse markedly diminished; both feet cool with marked color changes present; nail absent (surgically) from 3rd right toe and a large ulcer present in the nail bed; calcification of larger arteries in lower extremities present by x-ray	Right lumbar sympathectomy, L ₂ , L ₃	Ulcer healed promptly after operation; about 50 per cent improvement in claudication time on right with less color changes; right foot is warm and dry; requests operation on left side; not smoking
xviii	N. W.	34	Migratory phlebitis, left leg; claudication in left leg within 2-3 blocks of walking	14 mo.	Both feet cool and hyperhidrotic; moderate color changes present in the left foot; both dorsalis pedis and posterior tibial pulses absent on left with retarded vein filling	Left lumbar sympathectomy, L ₁ , L ₂ , L ₃	Early relief of claudication and reversal of color changes; return of claudication after 3 mo.; area of sweating noted about the inner aspect of left knee; has never ceased smoking completely
xix	A. Z.	38	Bilateral claudication and swelling; color changes and ulceration of left foot	3 yr.	Gangrene of the tips of the 4th and 5th toes left foot; absent posterior tibial and dorsalis pedis pulses bilaterally; marked color changes and hyperhidrosis; left calf 2 cm. less in diameter than right	Bilateral lumbar sympathectomy, L ₂ , L ₃ , L ₄	Prompt reversal of color changes and progressive loss of claudication; feet warm and dry; no change in pulsations; asymptomatic; not smoking

excellent progress noted initially after operation:

CASE XVIII. Nathan W., a thirty-four year old white male, had received a medical discharge from the U. S. Navy in July, 1945 because of phlebitis. He had been treated with paravertebral sympathetic block and ligation of the left saphenous vein. Upon discharge from the Navy he noted that he had severe cramping pain in the left calf after walking two or three blocks, and the physician whom he consulted suggested the diagnosis of thromboangiitis obliterans and advised him to cease smoking. Upon admission to this clinic positive physical findings were limited to the peripheral vascular system. Both lower extremities, especially the feet, were noted to be cool and hyperhidrotic. Moderate color changes were noted in the left foot on elevation and depression. The posterior tibial and dorsalis pedis arteries were impalpable on the left and the lower extremities exhibited decreased oscillometric readings. Vein filling in the left foot was noticeably retarded. Since paravertebral blocks, L₁ to L₃, caused the left foot to become warm, dry and pink, with diminution of claudication time and since the usual medical therapy over a period of two months resulted in no clinical improvement, the patient was subjected to left lumbar sympathectomy. (Table I.) Immediate results were good. The patient was ambulatory after the fifth day and was gratified to note the progressive decrease in calf claudication and reversal of color changes. Although he professed to have stopped smoking, at no time did he cease for more than two or three days. Three weeks after operation he again began to complain of the left calf and an area of sweating was noted about the left knee.

This case illustrates two facts which may detract from the otherwise good results of sympathectomy: One, of course, is the continued use of tobacco and the other is evidence of incomplete sympathectomy. However, it is our impression that the latter contributes little to the recurrences of this patient's symptoms.

That the superficial circulation in an extremity is enhanced after sympathectomy has been shown in excellent plethysmographic studies by Abramson,¹⁵ among others. However, it is not correct to infer

from such studies, as some have done, that augmentation of the superficial circulation occurs at the expense of the deep blood flow after sympathectomy. In fact, Goetz¹⁶ using his exquisite digital plethysmographic technique, has recorded changes in his patients indicating increase in deep blood flow after sympathectomy. Of his twenty-nine patients followed one to eleven years after operation, none showed any decrease in augmented blood flow achieved by sympathectomy. Using forearm plethysmography with certain ingenious auxiliary technics, Barcroft and Edholm¹⁰ in a recent report have concluded that blood flow in muscles of normal individuals is more than doubled by the release of sympathetic tone. In addition they reported that vasoconstrictor tone may gradually return to the blood vessels of sympathectomized subjects. The latter observation is contrary to the experiences of Goetz and not in evidence in our own patients at this time. It may be that Barcroft and Edholm are referring to the return of local vasomotor tone and not that mediated through sympathetic fibers.* In this latter opinion we concur. It has been our impression that the majority of patients suffering from thromboangiitis obliterans characteristically have high vascular tone. Protection of the young collateral circulation from vasoconstricting influences is of prime importance in the acute phase of this disease, and a permanent protecting influence is obtained by interruption of the sympathetic pathways.

As a rule the psychosomatic aspects of thromboangiitis obliterans have been given little attention in previous studies. Since this disease engenders so much economic debility with prolonged medical treatment, it is not remarkable that these patients often present a negative attitude and are inclined to be anxious and tense. That these functional expressions in turn may influence the speed of recovery and may initiate vasoconstricting stimuli to the extremities is

* In a personal communication Professor Barcroft has clarified this point by stating that he refers to return of local vasomotor tone.

not beyond our comprehension of the integration of functional and organic disease. The effect of a chain of constrictor impulses, such as just mentioned, on the blood supply to a digit has recently been demonstrated by Goetz¹⁶ in digital plethysmographic studies. Weiss¹⁷ has reported on a case of psychogenic peripheral vasospasm simulating organic vascular disease and he was able to obtain complete reversal of symptomatology in his patient by appropriate psychotherapy. It is of interest to speculate on the course of the disease in Weiss's patient if he had not proven to be amenable to psychotherapy. To us, therefore, interruption of the pathways carrying vasoconstricting impulses appears to be a good prophylactic measure in thromboangiitis obliterans when high vasoconstrictor tone is demonstrated. Since few reports previously written on this subject have contained a careful re-evaluation of patients at the end of two years, this series of cases with such favorable early and late results is submitted to substantiate this statement.

SUMMARY

1. The methods of study, distribution of patients and results of sympathectomy in nineteen cases of thromboangiitis obliterans are discussed.

2. Evidence supporting the view that sympathectomy increases deep blood flow to an extremity is reviewed.

CONCLUSION

Sympathectomy in properly selected cases of thromboangiitis obliterans causes early relief of symptoms as well as rapid rehabilitation of the patient, as noted in our two-year re-evaluation and follow-up. No deleterious effects resulting from this operation have been noted in this series. The disturbances in sexual function that may arise because of the operative procedure have been discussed.

REFERENCES

1. GOODMAN, E. N., MESSINGER, W. J. and WHITE, J. C. Indications and results of surgery of the autonomic nervous system in naval personnel. *Ann. Surg.*, 124: 204, 1946.
2. LYONS, R. H., MOE, G. K., NELIGH, R. B., HOOBLER, S. W., CAMPBELL, K. N., BERRY, R. L. and RENNICK, B. R. The effects of blockage of the autonomic ganglia in man with tetraethylammonium. *Am. J. M. Sci.*, 213: 315, 1947.
3. HITZROT, L. H., NAIDE, M. and LANDIS, E. M. Intermittent claudication studied by a graphic method. *Am. Heart J.*, 11: 513, 1936.
4. NAIDE, M., SAYEN, A. and COMROE, B. I. Characteristic vascular pattern in patients with rheumatoid arthritis. *Arch. Int. Med.*, 76: 139, 1945.
5. FREEMAN, N. E. The diagnosis and treatment of thrombo-angiitis obliterans in the vascular centers of Army General Hospitals. *Am. Heart J.*, 33: 332, 1947.
6. WHITE, J. C. and SMITHWICK, R. H. The Autonomic Nervous System, 2nd ed. The Macmillan Co., New York, 1941.
7. SILBERT, S. Treatment of thrombo-angiitis obliterans. *Hebrew M. J.*, 1: 3-11, 1942.
8. FRIEDLANDER, M., SILBERT, S., BIERMAN, W. and LASKEY, N. Differences in temperature of skin and muscles of the lower extremities following various procedures. *Proc. Soc. Exper. Biol. & Med.*, 38: 150, 1938.
9. WILKINS, R. W. Sympathetic Nervous Control of the Peripheral Vascular System, *Advances in Internal Medicine*. Vol. 1. New York, 1942. Interscience Publishers, Inc.
10. BARCROFT, H. and EDHOLM, O. G. Sympathetic control of blood vessels of human skeletal muscle. *Lancet*, 15: 513, 1946.
11. HARRIS, R. I. The role of sympathectomy in the treatment of peripheral vascular disease. *Brit. J. Surg.*, 23: 414, 1935.
12. FREEMAN, N. E. and MONTGOMERY, M. Lumbar sympathectomy in the treatment of intermittent claudication: selection of cases by claudication test with lumbar paravertebral procaine injection. *Am. Heart J.*, 23: 224, 1942.
13. LERICHE, R. and FONTAINE, R. Einige Bemerkungen über 1199 Operationen am Sympathikus. *Arch. f. klin. Chir.*, 186: 338, 1946.
14. DETAKATS, G. The value of sympathectomy in the treatment of Buerger's disease. *Surg., Gynec. & Obst.*, 79: 359, 1944.
15. ABRAMSON, D. I. Vascular Responses in the Extremities of Man in Health and Disease. Chicago, 1944. Univ. Chicago Press.
16. GOETZ, R. H. The rate and control of the blood flow through the skin of the lower extremities. *Am. Heart J.*, 31: 146, 1946.
17. WEISS, E. J. Psychogenic peripheral vasospasm. *Psychosom. Med.*, 8: 274, 1946.

Consideration of Glomerular Nephritis in Its Relation to Sulfonamide Sensitivity*

R. H. RIGDON, M.D., W. H. SIDDON, M.D. and D. E. FLETCHER, Ph.D.

Galveston, Texas

Little Rock, Arkansas

ALTHOUGH the etiology in every case of glomerular nephritis may not be established, it is widely accepted today that there is some relationship between streptococcus infections and glomerular nephritis. A non-suppurative type of inflammatory reaction occurs within the kidney which according to Forbus¹ "is probably always secondary to some other pathological processes even though the primary affection may be so hidden as to remain undiscovered." The experimental studies of Longcope and his associates^{2,3} and Long and Finner⁴ suggest that the renal lesion results from a process of sensitization, or an allergic type of reaction.

Experimental and clinical studies by many investigators have emphasized that sensitivity to sulfa drugs frequently occurs in man. The pathologic lesions that constitute this reaction indicate that it may occur in a variety of tissues, among which may be mentioned skin, blood vessels, heart, kidneys, liver, spleen and lungs.⁵⁻⁹ The similarity of this reaction to the sensitivity reaction produced by horse serum and certain chemical compounds has been pointed out.^{5,10-12}

The specific nature of antigenic substances is now well recognized and this characteristic depends upon their chemical composition. Immunologically active antigens may be produced by conjugating pure chemicals with animal serum proteins or other proteins. The specificity of the antigen depends upon the chemical radical and not upon the protein of the conjugated antigen.^{12,13} It has been shown that follow-

ing development of sensitization by repeated contact with certain chemicals, anaphylaxis may occur following further contact.^{14,15}

The question arises, in this problem of sensitization, whether there is experimental or clinical evidence to indicate that if the serum of one person conjugates with a compound to form an antigenic substance, is it more likely that the serum of this same person will conjugate more readily with another compound to form a second antigenic substance than will the serum of an individual who failed to conjugate with the first compound to form an antigenic substance? In other words, is there evidence to indicate that an individual is more likely to become hypersensitive to a second antigen than a person who never showed any sensitization reactions?

Rackemann¹⁶ in 1945 asked the questions "What is the allergic individual? Why is it that only a few persons become clinically sensitive? How many patients who suffer from eczema in childhood develop other manifestations of allergy: hay fever in their teens, asthma in their twenties, or possibly migraine later on? Are those the same individuals who as they grow older manifest reactions to penicillin, to the sulfonamide or perhaps get into trouble with dermatitis or industrial asthma? In other words, must we not regard the 'asthmatic state' as dependent upon a physiologic change and regard the 'allergic individual' as having something about him which is basic and fundamental and which last all through life."

Although hypersensitivity to a single

* From the Departments of Pathology and Medicine, University of Arkansas School of Medicine, Little Rock, Ark.

antigen is the rule, we sometimes see a patient who is sensitive to more than one antigen. More and associates⁷ reported a case (No. 18) in which sulfathiazole "appeared to induce asthmatic attacks" in a patient who gave a history of asthma. Rackemann and Green¹⁷ have observed eight cases of periarthritis nodosa associated with bronchial asthma and found a history of asthma in 8 per cent of 229 cases of periarthritis nodosa reported in the literature. Riemann and associates¹⁸ observed periarthritis nodosa in two patients who had trichinosis and they suggested a relationship with the high degree of sensitivity that develops to the trichina antigen. Individuals supposedly sensitive to horse serum may react quite differently when small amounts of the same form of antisera derived from different animal species are injected intramedially.¹⁹ Nelson²⁰ observed that in a patient sensitized to sulfathiazole an acute febrile reaction may occur following administration of sulfadiazine and sulfapyridine. Rich^{8,9} in his studies on periarthritis nodosa described eight cases in which this lesion was found at autopsy in patients who had hypersensitive reactions resulting from foreign serum and sulfonamide therapy. Rich⁸ stated "that widely different sensitizing antigens can be responsible for the development of the vascular lesions in different patients. It is not improbable that bacterial antigens may be concerned in some cases." Should one consider it merely a coincidence that of five of Rich's patients who shortly before death had sensitivity reactions following therapeutic injections of foreign serum, four also had received sulfonamides?

Any hypothesis as to the relationship of glomerular nephritis associated with a streptococcus infection and sulfa sensitivity may be difficult to establish either clinically or pathologically. However, a recent pathologic study of three cases has emphasized the need to consider such a hypothesis. These cases also indicate the necessity for caution in use of the sulfa drugs when there is a history of sensitivity to any antigen. In

two of these three subjects streptococci were isolated from the blood and cocci were demonstrated on the heart valves. Both patients had a progressive type of intracapillary glomerular nephritis. The third patient gave a history of "flu" and swelling of many joints, petechiae, nausea, vomiting and severe anemia. Typical lesions of glomerular nephritis were present. In each of these three cases there were pathologic lesions similar to those resulting from hypersensitivity to sulfa drugs.

CASE REPORTS

CASE I. The patient, a white female aged thirty-five years, was admitted to the University Hospital with the chief complaint of stiffness and pain in the joints "for four months." This illness began with flu and involvement of the joints followed within a month. The right hip became stiff and soon thereafter all extremities were involved. The fingers were stiff and numb. The tendons along the dorsum of the hands and feet were painful and red streaks developed along these surfaces. The pain was severe enough to make the patient "feel like screaming."

The patient thinks there was a little fever at times. She had epistaxis and spat up blood on several occasions. There was some shortness of breath and "smothering spells" following exertion. The heart was noted to beat fast at times and a sensation of "flutter" was observed over the precordium.

Approximately two months following onset of symptoms the patient said she was given "sulfa" for the "flu." She developed nausea, vomiting, rash and dizziness following this course of therapy. Approximately one month later she developed an "awful cutting pain" in the chest. A sulfa drug was given the following day. Nausea and vomiting occurred. Only six tablets were taken. Ten days later she developed itching of her fingers and feet. A rash developed on the hands, arms and lower extremities, which persisted for forty-eight hours. A few small nodules were observed by the patient on the skin about the elbows. These would appear and disappear according to the history.

The patient said that she had been anemic since she was sixteen. An appendectomy was performed when she was twenty-five. Tonsillitis occurred during childhood; there was no history of rheumatic fever. There were two miscarriages

before she delivered a live child. A second baby was born eight months preceding onset of her present illness. There was a history of arthritis in two of her sisters whose ages were not given. There was no history of sensitivity in this patient.

Upon physical examination the patient was observed to be apathetic and appeared ill. Pain occurred upon movement of the extremities. There was neither swelling nor an increase in temperature of the joints. The heart was normal in size and the sounds were distant and weak. Nothing abnormal was noted during examination of the chest. The temperature was 97.8°F., pulse, 84 per minute and respiration, 20 per minute. The systolic pressure was 115 mm. of Hg and diastolic was 75 mm. Hg.

The specific gravity of four specimens of urine varied between 1.009 and 1.010. A few white blood cells and 6 to 15 red cells per high power field were present. Only a trace of albumin was found. The non-protein nitrogen was 200 mg. per cent four days preceding death. The total plasma protein at this time was 6.5 Gm. per cent with the A/G ratio 1.38. The creatinine was 4.7 mg. per cent. The day preceding death the non-protein nitrogen was 225 mg. per cent, creatinine 5.3 mg. per cent and blood sodium chloride 430 mg. per cent. The phenolsulfonphthalein test was negative for dye in all samples.

The patient was anemic on admission and two days later the red cell count was 1.51 million, hemoglobin 4.2 Gm. and the hematocrit reading was 14 per cent packed cells. Color index was 0.93 and the volume index 1.16. The white blood cell count was 18,050 and platelet count was 51,340. The reticulocyte count was 1.3 per cent while the icteric index was 5.6. Coagulation and retraction times were normal.

A sternal bone marrow aspiration biopsy showed general hyperplasia. Cells of the erythrocytic series were prominent, constituting about 30 per cent of the total nucleated forms. Polychromatophilic erythroblasts were conspicuous by their presence. Several megakaryocytes were present. Several mitotic figures were seen which probably also indicate a hyperplastic state of the tissue. These findings apparently do not fit into any definite pattern. The anemia was practically normocytic and normochromic. It was suggested that "the bone marrow was acted upon by some active depressant which was responsible for the anemia, and



FIG. 1. Case 1. A, there is an increase in the number of cells infiltrating the mitral valve. Sometimes these cells are in small groups adjacent to the endocardial surface. B, the cells present in the mitral valve are usually mononuclear; however, few polymorphonuclear leukocytes are present. No bacteria are present; hematoxylin and eosin stain.

our studies were made at a time when the hematopoietic tissue was in violent, but ineffective, efforts of regeneration."

The patient remained in the hospital for eleven days during which time the joint pain persisted. The temperature was not elevated. She was given transfusions of whole blood on

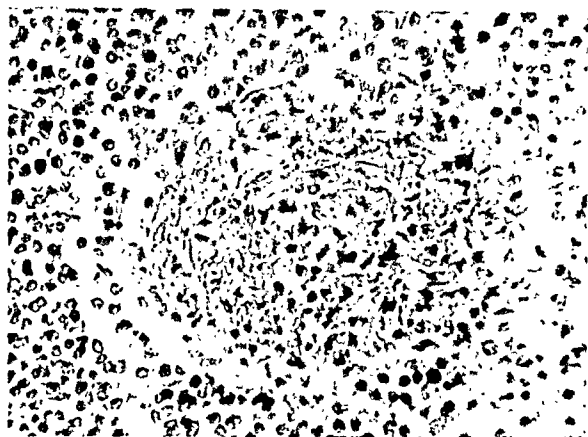


FIG. 2. Case 1. The walls of many of the blood vessels within the spleen are edematous and fragmented. Portions of the vessel wall stain deeply with eosin. Some of the vessel walls have mononuclear and polymorphonuclear cells infiltrating them; hematoxylin and eosin stain.

several occasions and frequently reacted to them with slight chills and an elevated temperature.

Pathologic examination revealed that the skin had a pale yellow color. Several petechiae were present in the skin over the buttocks. The serous cavities were filled with straw colored fluid, 1,000 cc. in the abdominal, 1,000 cc. in the right and 500 cc. in the left pleural cavity and 30 cc. in the pericardial sac.

The heart weighed 300 Gm. A fine granular exudate covered the visceral layer of pericardium. A few petechiae were present in the endocardium, myocardium and pericardium. The right ventricle was moderately dilated. No gross lesions were observed in the endocardium although microscopically the mitral valve was infiltrated with a moderate number of mononuclear cells and a few polymorphonuclear leukocytes. (Fig. 1.) Small areas of fibrinoid-like tissue were present within the valve.

The lungs were edematous and there were many areas of bronchopneumonia and also focal areas of fibrosis within the alveoli. There were areas of hemorrhage within the lung tissue. The liver weighed 1,850 Gm. The hepatic cells were swollen and there were small focal areas of fat within the liver tissue.

The spleen weighed 230 Gm. There was an apparent increase in the number of mononuclear cells within the pulp. The walls of some of the smaller blood vessels were fragmented and fibrinoid tissue was present. Mononuclear cells and polymorphonuclear leukocytes infiltrated these vessel walls and the adjacent stroma. Sometimes this degenerative process appeared

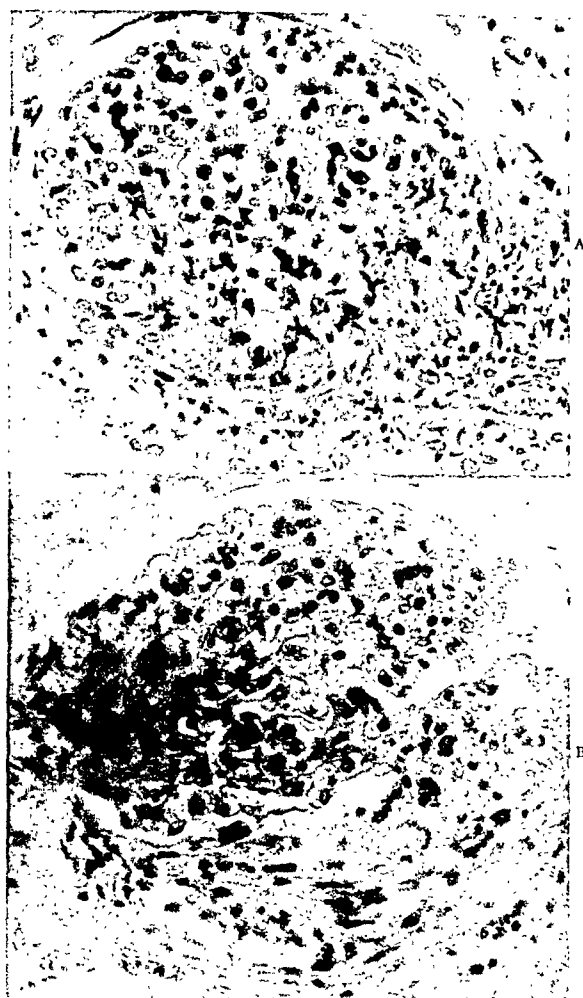


FIG. 3. Case 1. A, there is a proliferation of cells within the tuft and many have polymorphonuclear leukocytes in the tuft and in Bowman's space. Within many of the tufts are masses of a deep, eosin-staining material. Some of the glomeruli have many polymorphonuclear leukocytes and mononuclear cells infiltrating the wall and surrounding the entering arteriole; hematoxylin and eosin stain. B, some of the glomeruli are partially fibrotic while others are completely fibrotic; hematoxylin and eosin stain.

to involve the fibrous septa in the spleen. (Fig. 2.)

There were several small ulcerated areas in the mucosa of the cecum and colon. The degenerative and inflammatory reaction extended down into the submucosa.

The combined weight of the kidneys was 390 Gm. There were many petechiae in the cortex and also focal areas which appeared slightly yellow in color. Many of the glomeruli were completely fibrosed while others were partially scarred. (Fig. 3.) There was an increase in the cellular elements of the remaining tufts such as that observed in intracapillary glomeru-

lar nephritis. A few of the glomeruli showed a large number of mononuclear and polymorphonuclear leukocytes within the tuft. The wall of an occasional entering arteriole was infiltrated by similar cells. (Fig. 3A.) Red blood cells and leukocytes were present in Bowman's space and they filled the lumen of many tubules. Albuminous casts were present in the lumen of the tubules; the epithelial cells lining the convoluted portion of the tubules usually were low and stained deeply with hematoxylin. There were a moderate number of mononuclear cells infiltrating the stroma between the renal tubules.

Anatomic Diagnosis: (History of sulfa therapy on two occasions with symptoms of hypersensitivity); periarteritis nodosa involving the arteries in the spleen; petechiae in endocardium, myocardium and pericardium; chronic inflammatory reaction in mitral valve; acute and chronic intracapillary glomerular nephritis; acute pericarditis and acute ulcerations in area of cecum. (History of uremia); moderate dilatation of right ventricle; ascites, 1,000 cc.; hydrothorax, left 500 cc. and right 1,000 cc.; splenomegaly; ecchymosis of the left buttock; bronchopneumonia; focal areas of chronic pneumonia.

Comment: As far as is known this woman was in perfect health until she developed a pulmonary infection approximately four months preceding death. Subsequent to the first infection pain and swelling of the joints occurred. Sulfa was given on two occasions. Nausea, vomiting and petechiae of the skin occurred following the second course of therapy. When she entered the University Hospital eleven days before death, there was severe anemia and laboratory findings indicative of renal failure.

The inflammatory reaction involving the mitral valve certainly suggests an early acute rheumatic process. Necrosis and cellular reaction in the septa of the spleen are similar to the lesions described by More and associates⁷ in patients showing sulfa sensitivity. Glomerular lesions, inflammatory reaction on the mitral valve and necrosis in the spleen, each suggest a hypersensitive reaction. The renal lesions according to the patient's history developed within a period of four months. Usually hyper-

trophy of the left ventricle and hypertension occur in patients who live to be thirty-five years of age before developing renal insufficiency when the nephritic process begins in childhood. The majority of glomeruli showed the typical lesions of glomerular nephritis. The few glomeruli that showed a fibrinoid material and an infiltration of leukocytes and mononuclear cells within the tuft reminded us of the similarity of this renal lesion to the vascular lesions in the spleen.

Clinically, there was nothing to suggest a bacterial infection in this patient and furthermore nothing was found at autopsy to indicate an infection. Active glomerular lesions do occur in cases of chronic glomerular nephritis; however, it is suggested that in this patient some of the glomerular lesions may have been a part of the hypersensitive reaction to the sulfa drugs. The mitral lesion at this time was more likely that of acute rheumatic fever; however, it is significant to find this variety of hypersensitive reactions in one individual. Recently one of us (R. H. R.) saw a case of sulfa sensitivity in a white female approximately sixty-five years of age. Acute arthritis with subsequent myocardial damage followed the skin manifestation of hypersensitivity within a period of two weeks.

CASE II. The patient, a thirty-nine year old white male, was admitted to the University Hospital with a history of high fever and pain in the chest three weeks preceding time of death. Onset of this illness was two months previously at which time he became nauseated and vomited while at work. That night he thought that he had some fever. He was unable to work for a week; however, he returned to work the second week although he was weak and lethargic. He had fever during this period. A month following onset of illness he was hospitalized and roentgenologic examination of the chest showed changes interpreted as "suspicious lesions that should be carefully watched." The temperature was high and it spiked daily. There was an increase in the degree of shortness of breath. The patient noticed that his urine was blood-tinged.

On admission the patient was acutely ill. The temperature was 102.4°F., pulse 130 per minute, respiration 26 per minute and the systolic blood pressure 130 mm. Hg and the diastolic pressure 80 mm. Hg. The skin was hot, moist and pale. Respirations were chiefly abdominal in type. There was dullness over the right lower lobe and fine moist râles were present over both lungs.

The urine contained a 2 to 4 plus albumin and two days before death many red blood cells were present. The non-protein nitrogen was 100 mg. per cent three days preceding death. At this time the creatinine was 2.3 mg. per cent, plasma proteins 8.36 Gm. per cent, albumin 3.09 Gm. per cent, globulin 5.27 Gm. per cent and the A/G ratio was 0.59. On admission there was anemia with only 2.62 million red blood cells and a hemoglobin of 58 per cent. The white blood cell count was 8,850. Both the red and white cell counts remained low in spite of several transfusions of whole blood. A non-hemolytic streptococcus was isolated from the blood stream ten days preceding death and a second positive culture was obtained a few days after the first.

During the period of hospitalization a coarse presystolic and systolic murmur developed over the mitral area. Dilatation of the right and left ventricle subsequently occurred, accompanied by pulmonary and peripheral edema. Classical signs of right pleural effusion developed. Death followed an episode of acute respiratory difficulty.

The patient, while in the University Hospital, was treated with large doses of penicillin. Sulfadiazine was given only twice on the seventeenth day preceding death. No clinical reactions to the sulfa were noted. The patient had received sulfathiazole, however, approximately seventy days previously for a period of eight days.

Pathologic examination revealed the following: There was a small amount of edema of the lower extremities; 1,000 cc. of straw colored fluid was present in the peritoneal cavity and 800 cc. of a slightly turbid fluid was present in the right pleural cavity.

The heart was large as a result of dilatation of both the right and left ventricles. The myocardium was pale and flabby. Multiple polypoid vegetations arose from the auricular surface of the tricuspid valve; some of these were 2.0 cm. in diameter; they were soft and friable. There was nothing on the tricuspid valve or the other

valves of the heart to suggest a lesion older than the acute endocarditis. Innumerable gram-positive cocci were embedded in the necrotic tissue of the valve.

The right lung was atelectatic as a result of the presence of fluid in the cavity. Multiple infarcts were present in both lungs, these varied both in age and in size. Many of the branches of the pulmonary artery were occluded by infected emboli.

The liver weighed 2,175 Gm. and showed the typical changes of chronic passive congestion. The spleen weighed 530 Gm.; it was soft in consistency. A few petechiae were present in the mucosa of the gastrointestinal tract. Histologically, the wall of several of the small arteries in the submucosa appeared coagulated and they were surrounded by a collection of inflammatory cells, mostly of the mononuclear variety. (Fig. 4A.)

The kidneys together weighed 515 Gm. Many petechiae were present in the cortex. There were small focal yellow areas throughout the cortex which represented tubular degeneration. The lumen of many of the tubules and some of the tufts were filled with red blood cells. There was a marked increase in the number of cells in the glomeruli which apparently were endothelial cells. Few leukocytes and mononuclear cells also were present in some of the glomeruli. An occasional glomerulus had either a fibrous adhesion or a proliferation of epithelial cells between its tufts and capsule. There was some edema of the interstitial tissue of the kidney and a moderate number of mononuclear cells were present. An occasional eosinophile was present in the interstitial tissue.

Anatomic Diagnosis: (History of acute bacterial endocarditis due to a non-hemolytic streptococcus); acute bacterial endocarditis involving the tricuspid valve; dilatation of cavities of the heart; emboli in branches of pulmonary artery; multiple infected infarcts in both lungs; chronic passive congestion of viscera; ascites 1,000 cc. pleural effusion, right 800 cc.; atelectasis of right lungs; edema of lower extremities; acute splenic tumor; acute and subacute intracapillary glomerular nephritis; periarteritis nodosa involving arteries in colon; (history of sulfa therapy); atrophy of testicle; healed pulmonary tuberculosis; fibrous pleural adhesions.

Comment: The patient was sick for approximately three months with elevated

temperature and dyspnea. When admitted to the University Hospital three weeks preceding time of death, a non-hemolytic streptococcus was isolated from the blood on two occasions. There was severe anemia at this time and retention of non-protein nitrogen. The urine showed 2 plus albumin.

The pathologic changes on the tricuspid valve were typical of acute bacterial endocarditis. There was no evidence in this heart of an old rheumatic process; furthermore, there was no history of such an infection. The kidneys were typical of the so-called intracapillary type of glomerular nephritis. The process was active as indicated by the presence of red blood cells within the lumen of many of the tubules. There were no embolic phenomena observed in any of the viscera except the lungs. Apparently all of the infected emboli were filtered out by the lungs.

The lesions in the blood vessels of the colon were identical with those of periarteritis nodosa as described by Rich.^{8,9} No other pathologic changes were observed in the blood vessels to indicate a sensitivity reaction. The last dose of sulfa this patient received was sulfadiazine seventeen days before death. It would seem more likely that the intracapillary glomerular nephritis was associated with the streptococcus infection rather than with the sulfa therapy.

CASE III. The patient, a white female aged seventeen, was admitted to the University Hospital with a history of hematuria, nausea and vomiting and during the previous two days there were periods during which she was irrational. Ten weeks previously she stuck a nail into her foot. Home remedies were used for two weeks at which time she consulted a physician who gave her sulfa. The infection in her foot improved; however, she developed a cold and sore throat which necessitated bed rest. During this time there was a backache and headache.

Two weeks prior to the time of hospitalization she developed another cold, sore throat and fever. She was given two tablets of sulfa every four hours for twelve days. Nausea and vomiting began before this course of therapy was completed. Two days before admission the urine was thought to contain blood and a few pete-

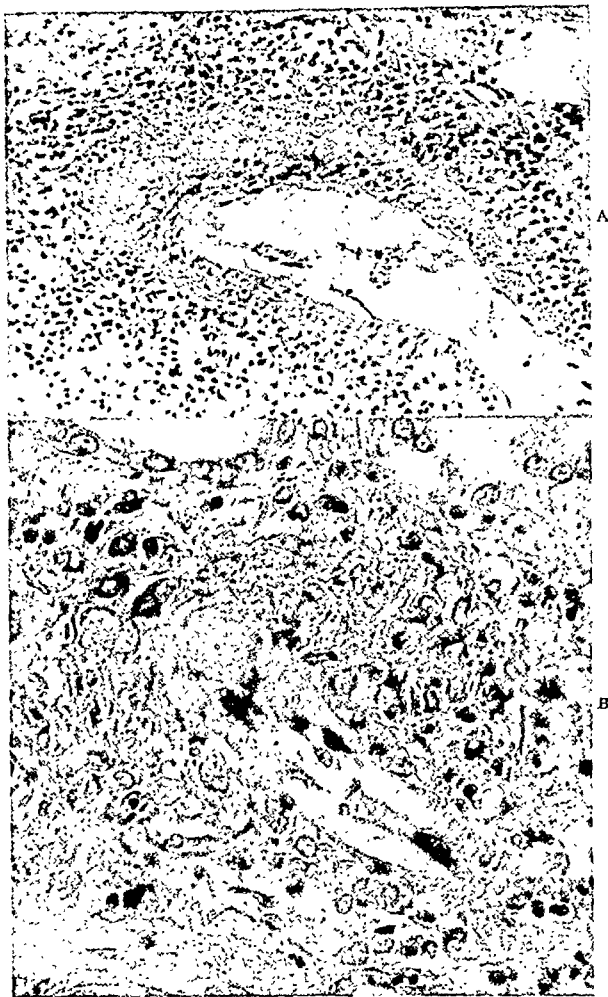


FIG. 4. A, this illustrates the typical periarteritis nodosa lesion which is present in the colon. No bacteria were demonstrated in this lesion; hematoxylin and eosin stain (Case II). B, a portion of the wall of this vessel in the kidney is necrotic. The vessel wall and the surrounding tissues are infiltrated with mononuclear cells; hematoxylin and eosin stain (Case III).

chiae appeared in the skin over the breast. Two years previously an illness occurred characterized by hematuria, headaches and lumbar pain. Since this time, edema of the face had been observed in the mornings.

On physical examination the systolic blood pressure was found to be 142 mm. Hg and the diastolic 90 mm. Hg, the pulse 92 per minute, respiration 24 per minute and the temperature 100°F. Her face was edematous and she appeared anemic and acutely ill. Petechiae were present over the breast. Numerous small "moth eaten" areas were present in the retina. The nasal mucosa was ulcerated bilaterally. The heart was normal in size and a harsh systolic murmur could be heard over the entire precordium; it was loudest at the apex.



FIG. 5. Case III. A, Bowman's space and the lumen of many of the tubules are filled with red blood cells. The cells lining the convoluted portion of the tubules are cuboidal and stain deeply with hematoxylin. Collections of mononuclear cells, among which are eosinophiles, are present in the interstitial tissue; hematoxylin and eosin stain. B, the glomeruli show a marked proliferation of cells within the tuft. Essentially all the glomeruli are like this one; hematoxylin and eosin stain.

During the ten days of hospitalization the specific gravity of the urine varied between 1.010 and 1.020. There usually were 12 to 20 red blood cells and 3 to 5 white blood cells per high power field. Red blood cell count on admission was only 2.44 million and hemoglobin was 68 per cent. White blood cell count was 16,550 with 82 per cent polymorphonuclear leukocytes, 1 per cent stabs, 14 per cent lymphocytes and 3 per cent monocytes. The white blood cell count varied very little during the period of hospitalization. The red cell count increased following transfusions. On admission non-protein nitrogen was 168 mg. per cent and two days before death it was 167 mg. per cent, albumin 3.59 Gm. per cent, globulin 2.57 Gm. per cent, A/G ratio 1.40 and total protein 6.16 Gm. per cent. On the day preceding death

creatinine was 3.53 per cent, blood sodium chloride 402 mg. per cent and carbon dioxide combining power 64 volumes per cent.

Three transfusions of whole blood and 20,000 units of penicillin every three hours were given during the ten days that she remained in the hospital. A pericardial friction rub was observed the day preceding death and on the day of death the urine was grossly bloody.

Pathologic study revealed the following: A few petechiae were present in the skin and there was some edema of the lower extremities. Straw colored fluid was present in the serous cavities, 2,000 cc. in the peritoneal cavity, 200 cc. on each side of the thoracic cavity and 100 cc. in the pericardial cavity.

The heart was normal in weight and the cavities were dilated; the musculature was pale and flabby. There was an area of acute reaction over the surface of the right atrium. Large friable vegetations were present on the leaflets of the pulmonary valve. The infection had extended to the adjacent endocardium and into the pulmonary artery. Gram-positive cocci were present in the necrotic vegetations. Cultures were positive for streptococcus viridans.

The lumens of many of the branches of the pulmonary artery were filled with infected emboli. Many infarcts were present in both lungs, these varied both in age and in size.

The liver extended 4 fingerbreadths below the right costal margin and showed the changes typical of chronic passive congestion. The spleen weighed 765 Gm. and it was soft in consistency. Small groups of hematopoietic cells were present in the pulp. A few petechiae and a few superficial ulcerations were present in the mucosa of the colon.

The kidneys together weighed 1,000 Gm. They were pale and edematous. Focal areas of tubular degeneration and small hemorrhages were present in the cortex. The lumen of many of the tubules were filled with red blood cells, casts and albumin. (Fig. 5A) All the glomerular tufts showed a marked increase in the number of endothelial-like cells. (Fig. 5B). An occasional fibrous adhesion was present between the tuft and Bowman's capsule. The renal interstitial tissue was edematous and diffusely infiltrated with mononuclear cells, some of which were eosinophilic. The walls of some of the small blood vessels in the kidneys were edematous, fragmented and necrotic. Mononuclear cells infiltrated the wall of such vessels and extended out into the surrounding tissue (Fig. 4B.)

Anatomic Diagnosis: (History of nail wound of foot four months previous to death; sulfa therapy with hypersensitive reaction; nephritis with uremia); acute bacterial endocarditis involving pulmonary valve with extension to adjacent endocardium and into the pulmonary artery (*streptococcus viridans*); localized area of acute pericarditis over right auricle; multiple infected emboli in branches of pulmonary artery; multiple infarcts in both lungs which vary widely in size and age; dilatation of right ventricle; ascites 2,000 cc.; hydrothorax, bilateral 200 cc.; hydropericardium 100 cc.; splenomegaly (765 Gm.); acute and subacute intracapillary glomerular nephritis; acute ulcerative colitis (uremic); periarteritis nodosa in renal vessels with mononuclear infiltration of interstitial tissue of the kidneys; (hypersensitive reaction of sulfa); petechiae in skin and viscera; generalized lymphadenitis of superficial lymph nodes; chronic cystitis; chronic cervicitis.

Comments: This girl apparently developed a streptococcus infection of the pulmonary valve as the result of the nail wound which occurred three months before death. She was treated with sulfa drugs on two occasions during this interval. No reaction occurred following the first course of sulfa therapy; however, when it was repeated approximately six weeks later, nausea, vomiting and petechiae occurred.

On admission to the University Hospital nine days preceding the time of death the clinical and laboratory findings were consistent with the diagnosis of nephritis accompanied by uremia. The pathologic lesions were typical of acute bacterial endocarditis involving the pulmonary valve. There was nothing to suggest either a previous injury to this valve or malformation. The renal lesion was that of intracapillary glomerular nephritis. The presence of red blood cells in the lumen of many of the tubules would indicate an active process. An interstitial reaction certainly occurs in both acute and subacute glomerular nephritis as observed in the cases of nephritis associated with scarlet fever. The significant feature, however, of the interstitial reaction in this patient is the presence of eosinophilic mononuclear cells. There were many groups of mononuclear

cells in the interstitial tissue. Such a reaction has been described by Lichtenstein and Fox,⁵ French⁶ and More and associates⁷ in cases of sulfa hypersensitivity. The presence of periarteritis nodosa-like lesions in the interstitial tissue of the kidneys apparently supports the rôle that sulfa sensitivity may have played in this case.

Glomerular and tubular lesions such as we have in this patient are similar to those accompanying streptococcus infection and are thought to be the result of sensitivity to this organism. The presence of periarteritis nodosa-like lesions in the interstitial tissue is indicative of a sensitivity reaction and in view of the frequency in which this lesion occurs following sulfa drugs it is suggested that in this case it is the result of the sulfa.

This case is of interest also from the standpoint of the infrequency of streptococcus infections involving the pulmonary valve. In four of the five cases cited by Rogers endocarditis was acute.²¹ Allen²² expressed the opinion that virulent organisms are more likely to produce acute lesions on the right side of the heart than avirulent ones. *Streptococcus viridans* usually produces a subacute type of endocarditis; however, Held and Goldbloom²³ have observed cases in which they considered the lesion to be produced by streptococcus *viridans* and considered it to be acute.

COMMENTS

Our interest in glomerular nephritis and sulfa sensitivity resulted from the observation that a majority of our patients showing hypersensitivity reactions, as observed at autopsy, also had glomerular nephritis. The total number of such cases, of course, is small; however, it will be of interest to determine if such a combination of lesions is merely a coincidental finding in these three patients.

As a result of both experimental and clinical observations it is now widely accepted that hypersensitivity to the streptococcus may manifest itself as glomerular nephritis, and hypersensitivity to sulfa drugs may manifest itself as an interstitial

renal lesion and periarteritis nodosa. The experimental studies of Rich and Gregory²⁴ emphasize this problem of sulfa sensitivity and glomerular nephritis. Three of five rabbits given both horse serum and sulfadiazine developed acute glomerular nephritis. The similarity of the renal changes in these rabbits to the glomerular lesions observed in our three patients is obvious from their description: "There was condensation of glomerular tufts with syncytial proliferation of the glomerular epithelium, hemorrhage in Bowman's capsule and in the tubules and albumin and casts in the tubules . . . The attack was upon the glomeruli independent of the arterioles." Hemorrhage in Bowman's space and blood within the tubules were found frequently in our three human cases. In commenting upon the experimental renal lesions, Rich and Gregory²⁴ say that "the glomerular lesions in our rabbits are of the same nature as the fresh glomerular lesions described by Longcope and attributed by him to anaphylactic hypersensitivity."

The same type of sensitivity reaction in blood vessels may occur following administration of horse serum, sulfa drugs and certain chemical compounds.^{10,12} In our first case it is interesting to observe the type of reaction within the glomeruli and that in the wall of the blood vessels in the spleen and in the mitral valve. In each of these three sites mononuclear and polymorphonuclear cells were present and also there were small focal areas of deep eosin-staining fibrinoid-like tissue. Our attention would not have been attracted to this glomerular change if there had not been both a clinical history of sulfa sensitivity and pathologic lesions elsewhere in the body consistent with hypersensitivity. The pathologic changes in the mitral valve would suggest an acute rheumatic lesion. However, Clark and Kaplan²⁵ observed a similar inflammatory process in the valves of a patient who died as the result of serum sickness. It is widely accepted at this time that acute rheumatic fever is the result of a hypersensitivity reaction. It is suggested that a similar lesion may occur in the

valves of the heart as a result of sulfa sensitivity, as has been described by Leary²⁶ in acute rheumatic endocarditis and Clark and Kaplan²⁵ in serum sickness. Friedberg and Gross²⁷ reported four cases in which periarteritis nodosa and rheumatic heart disease were associated. In one of these cases there were "glomerular lesions resembling those of subacute diffuse glomerulonephritis of the intracapillary type." In discussing these two processes they state: "In both instances one is dealing with a disease of unknown etiology. Both have been considered by definite groups of investigators to be the expression of an allergic reaction in a person sensitized to more than one agent rather than the result of infection by one specific organism." It would be of considerable interest at this time to know if these patients with periarteritis nodosa associated with rheumatic heart disease received any of the sulfa drugs.

Lichtwitz²⁸ has expressed the opinion that glomerular nephritis occurs infrequently with rheumatic fever. He says "though vascular allergy is an important feature of rheumatic pathology, glomerulonephritis, which frequently is an allergic disease, occurs in rheumatic fever so rarely as to suggest that the rheumatic attack on the joints or on the heart precludes a like attack on the kidney."

Cases II and III are similar in that both had acute bacterial endocarditis on the right side of the heart produced by streptococci. The glomerular lesions were identical. In each case there was evidence of periarteritis nodosa. Both patients were treated with sulfa drugs. From these two cases one cannot determine with any degree of certainty the rôle played by either sensitivity to the streptococcus or sensitivity to the sulfa therapy; however, it is interesting to find evidence of sensitivity to sulfa in these two cases of intracapillary glomerular nephritis. There also is evidence of sensitivity and intracapillary glomerular nephritis in Case I. It is suggested that care should be used in administering any of the sulfa drugs to patients who have a history of allergy; furthermore, the three cases

reported in this paper should emphasize its possible effect in cases of glomerular nephritis. Williams and associates²⁹ treated a small group of patients with acute glomerular nephritis with sulfanilamide in 1943 and concluded that their results were most satisfactory. Murphy and Wood³⁰ likewise obtained good results by treating a small group of patients with acute glomerular nephritis with sulfonamides. There is no record in the aforementioned studies that the patients had received sulfa previous to this treatment for nephritis. It may be shown subsequently that only a small percentage of patients with glomerular nephritis develop periarteritis nodosa; however, this relationship apparently deserves further study.

SUMMARY

Three cases are reported of glomerular nephritis in which there were other pathologic lesions similar to those reported in cases of sensitivity to sulfa drugs. In two of these streptococcic endocarditis was present on the right side of the heart. Since glomerular nephritis is considered to be the result of a sensitivity reaction, the problem of use of sulfa drugs in diseases resulting from hypersensitivity is discussed. It is pointed out that a patient who becomes sensitized to one antigen may also become sensitive to a second antigen. Because of this, sulfa drugs should be used more carefully.

REFERENCES

1. FORBUS, WILEY D. Reaction to Injury. Baltimore, 1943. Williams and Wilkins Company.
2. LONGCOPE, W. T. Production of experimental nephritis by repeated protein intoxication. *J. Exper. Med.*, 18: 678, 1913.
3. HANSEN, PRUSS O. G., LONGCOPE, W. T. and O'BRIEN, D. P. Skin reactions to filtrates of hemolytic streptococci in acute and subacute nephritis. *J. Clin. Investigation*, 7: 543, 1929.
4. LONG, E. R. and FINNER, L. L. Experimental glomerulonephritis produced by intrarenal tuberculin reaction. *Am. J. Path.*, 4: 571, 1928.
5. LICHTEINSTEIN, LOUIS and FOX, LEON J. Necrotizing arterial lesions resembling those of periarteritis nodosa and focal visceral necrosis following administration of sulfathiazole: report of a case. *Am. J. Path.*, 22: 665, 1946.
6. FRENCH, A. J. Hypersensitivity in the pathogenesis of the histopathologic changes associated with sulfanamide chemotherapy. *Am. J. Path.*, 22: 679, 1946.
7. MORE, ROBERT H., GARDNER, C., McMILLAN and DUFF, G. LYMAN. The pathology of sulfanamide allergy in man. *Am. J. Path.*, 22: 703, 1946.
8. RICH, A. R. The role of hypersensitivity in periarteritis nodosa. *Bull. Johns Hopkins Hosp.*, 71: 123, 1942.
9. RICH, A. R. Additional evidence of the role of hypersensitivity in the etiology of periarteritis nodosa. *Bull. Johns Hopkins Hosp.*, 71: 375, 1942.
10. RICH, A. R. The role of hypersensitivity in the pathogenesis of rheumatic fever and periarteritis nodosa. *Proc. Inst. Med. Chicago*, 15: 15, 1945.
11. MARINE, D. and BAUMANN, E. J. Periarteritis nodosa-like lesions in rats fed thiouracil. *Arch. Path.*, 39: 325, 1945.
12. LONGCOPE, W. T. Serum sickness and analogous reactions from certain drugs, particularly the sulfonamides. *Medicine*, 22: 251, 1943.
13. LANDSTEINER, K. Serologic and allergic reactions with chemical compounds. *New England J. Med.*, 215: 1199, 1936.
14. LANDSTEINER, K. and JACOBS, J. Studies on the sensitization of animals with chemical compounds. III. Anaphylaxis induced by arsphenamine. *J. Exper. Med.*, 64: 717, 1936.
15. HORSFALL, F. L. Formaldehyde hypersensitiveness: an experimental study. *J. Immunol.*, 27: 569, 1934.
16. RACKEMANN, FRANCIS M. Some future problems in allergy. *South. M. J.*, 39: 497, 1945.
17. RACKEMANN, F. M. and GREENE, J. E. Periarteritis nodosa and asthma. *Tr. A. Am. Physicians*, 54: 112, 118, 1939.
18. RIEMANN, HOBART A., ALISON, H. PRICE and PETER, A. HERBERT. Trichinosis and periarteritis nodosa. *J. A. M. A.*, 122: 274, 1943.
19. SEEGAL, B. C., KHORAZO, D. and MEHLMAN, JR. Local serum sickness in man following the intracutaneous injection of small amounts of antisera. *J. Allergy*, 7: 27, 1935.
20. NELSON, J. Acquired sensitivity of sulfanamide drugs. *J. A. M. A.*, 119: 560, 1942.
21. ROGERS, R. J. Subacute bacterial endocarditis confined to a pulmonic valve with malformed leaflets. *J. Lab. & Clin. Med.*, 29: 825, 1944.
22. ALLEN, A. C. Mechanism of localization implantation of vegetations of bacterial endocarditis in the heart. *Arch. Path.*, 27: 399, 1939.
23. HELD, I. W. and GOLDBLOOM, A. A. Acute streptococcus viridans endocarditis. *Arch. Int. Med.*, 53: 508, 1934.
24. RICH, ARNOLD R. and GREGORY, JOHN E. The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. *Bull. Johns Hopkins Hosp.*, 72: 65, 1943.
25. CLARK, E. and KAPLAN, B. I. Endocardial, arterial and other mesenchymal alterations associated with serum disease in man. *Arch. Path.*, 24: 458, 1937.
26. LEARY, TIMOTHY. Early lesions of rheumatic endocarditis. *Arch. Path.*, 13: 1, 1932.
27. FRIEDBERG, C. K. and GROSS, LOUIS. Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease. *Arch. Int. Med.*, 54: 170, 1943.
28. LICHTWITZ, LEOPOLD. Pathology and Therapy of Rheumatic Fever. New York, 1944. Grune and Stratton, Inc.

Chemotherapy of Malignant Disease*

ALFRED GELLHORN, M.D. and LOGAN O. JONES, M.D.

New York, New York

Charlotte, North Carolina

STRIKING advances in surgery and radiotherapy coupled with improved diagnosis of early malignancy have markedly reduced the mortality in malignant disease in recent years.¹ However, the majority of patients with cancer can be offered only palliation, usually in the form of nursing care, non-specific supportive measures and analgesics. The magnitude of the responsibility which the medical profession faces in this connection is indicated by the estimate that there are now more than 800,000 cases of malignancy in the United States and that 185,000 persons die of cancer in this country every year.² It has been further calculated that only 20 per cent of persons with malignant disease are salvaged for five years by the current methods of therapy. The need for a therapeutic approach to malignancy in addition to surgery and radiotherapy is apparent.

Purgation, irrational diets, blood-letting, escharotic pastes, heavy metals, snake venoms and hundreds of other ineffectual therapeutic regimens have been used in the past in the management of disseminated malignant disease. Critical laboratory and clinical evaluations of these measures have revealed their uselessness or even harmfulness and they have been largely discarded.

In the past forty years, however, there has been ever increasing research activity in the field of cancer chemotherapy. The rate at which advances have been made in this branch of experimental therapeutics in the past decade has been so rapid that it seems justifiable to anticipate, with guarded optimism, an entirely new therapeutic

approach to the problem of disseminated malignant disease.

It is the purpose of this paper to assemble the evidence that is available concerning a number of carcinolytic agents. It is hoped that a review of this subject will clarify the indications for certain chemotherapeutic agents of demonstrated value, and also provide a general background which may be useful in evaluating the significance of advances yet to be made.

PRODUCTS OF MICRO-ORGANISMS

Background and Rationale. During the past eighty years there has been continuous investigation of the effects on malignant cells of products of micro-organisms. In 1868 Busch³ reported on the dramatic regression of inoperable sarcomas in two patients coincident with an erysipelas infection. At this time the organism producing erysipelas had not yet been isolated so that efforts by Busch to produce erysipelas in other patients with malignant disease were unsuccessful. Following his demonstration of a streptococcus as the cause of erysipelas, Fehleisen⁴ injected cultures of these living organisms for the treatment of human cancer with encouraging results.

The experimental studies on bacterial products as carcinolytic agents was instituted by Spronck in 1892.⁵ Injecting sterile filtrates of "*Streptococcus erysipelas*" into dogs with spontaneous malignant tumors, he observed degenerative changes in a majority of the tumors. Beebe and Tracy in 1907⁶ extended the experimental in-

* From the Departments of Cancer Research and Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y. This survey was prepared in connection with work supported by the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

vestigations by using bacterial filtrates prepared from cultures of *Bacillus coli communis*, *Staphylococcus pyogenes aureus*, "*Str. pyogenes*" and *B. prodigiosus*, studying their effects on transplanted lymphosarcoma in dogs. Their results were provocative, in that softening of the tumors was noted frequently and occasional tumors regressed completely. In the succeeding quarter of a century there was little experimental activity in this approach to tumor chemotherapy, but interest was revived by the report of Gratia and Linz in 1931.⁷ These investigators had been studying the Shwartzman phenomenon under a variety of conditions and were impressed by the tissue localization which could be achieved by appropriate technic. They injected bacterial filtrate from *B. coli* directly into transplanted liposarcoma in guinea pigs. Twenty-four hours later the same filtrate was injected intravenously, following which they observed extensive hemorrhage and necrosis in the tumor masses but not in other tissues. In another series of experiments they discovered that it was not necessary to inject the filtrate into the tumors inasmuch as the same violent intratumor reaction occurred following intravenous injection alone. In the next year Shwartzman and Michailovsky⁸ reported that parenteral administration of a filtrate of meningococcus culture produced the same specific changes in mouse sarcoma 180 noted by Gratia and Linz. These observations were confirmed by Shear.^{9,10}

Following parenteral injection of a potent antitumor bacterial filtrate, progressive hemorrhage with histologic evidence of tumor disruption during the first twenty-four hours was noted. At this time, however, most of the malignant cells appeared viable. After twenty-four hours extensive necrosis of neoplastic cells was apparent. Gross observation showed the formation of a dry hemorrhagic scab with a surrounding zone of apparently active growth. In the course of seven to ten days the necrotic material sloughed leaving a bed of granulation tissue which in many instances went

on to complete healing. Microscopically, there was a sharp line of demarcation between necrotic tumor cells and actively proliferating cells. In the course of the week after injection all tumor cells within the necrotic circle became poorly stained or fragmented and disappeared.¹¹

Shear and his associates^{12,13} subsequently demonstrated that a filtrate of *Serratia marcescens* (*B. prodigiosus*) cultures is also a potent agent, inducing hemorrhage and necrosis in subcutaneous mouse carcinomas. Over a period of several years they fractionated and purified this material until an extremely active preparation was obtained which produced tumor hemorrhage and necrosis when injected into mice in dosages as small as 0.1 microgram.¹⁴ The highly purified fraction has been characterized chemically and has been found to be a polysaccharide.¹⁵ Shear and his co-workers have explored with thoroughness the potentialities and limitations of the hemorrhage-producing bacterial polysaccharide in the chemotherapy of experimental neoplasms. From their reports¹⁶ it can be concluded that the polysaccharide produces specific changes in a variety of tumors, including both transplanted and primary sarcomas as well as primary carcinomas. The toxicity of the polysaccharide was found to be greater in tumor-bearing mice than in normal animals, and the toxicity in the tumor mice was directly related to the size of the neoplasm being treated. Thus, it was demonstrated that the lethal effect in these mice was due to hemorrhage and necrosis in the tumor with secondary absorption of toxic products from tumor breakdown in addition to primary polysaccharide toxicity. It was noted further that some portion of the neoplasm almost invariably escaped destruction and that areas of tumor unaffected by the initial dose were resistant to the action of subsequent doses. In the few instances in which the entire tumor was involved in the hemorrhagic and necrotic process the animals developed signs of severe intoxication followed by shock and death.

Besides the observation that many species of bacteria are capable of elaborating substances which induce hemorrhage and necrosis in tumors, attention has been called to the fact that spirochetes causing relapsing fever (*Borrelia recurrentis*)¹⁷ and tick fever (*Bor. duttoni*)¹⁸ produce regressive effects in experimental tumors. Of particular interest because of its current clinical application, is the work of Roskin and his collaborators.¹⁹⁻²¹ These workers undertook a systematic study of the influence of various infections and toxins on transplanted cancer. They finally selected *Schizotrypanum cruzi* because they found that in mice the spirochete localized and proliferated chiefly in certain organs rather than in the blood stream, resulting in a more chronic course than was obtained with other experimental infections. They observed that when mice were infected with *S. cruzi* and at the same time inoculated with Ehrlich carcinoma the development of both the infection and the tumor was depressed as compared with control groups of mice. The natural course of simultaneous infection and malignancy in mice was a gradual increase in the infection with eventual death of the animals; in the terminal stages of the infection the tumor either markedly regressed or disappeared. From these experiments they concluded that the trypanosome infection exerted an antagonistic action on mouse cancer. However, since it was considered possible that the carcinolytic effect thus observed was a result of deprivation of nutrient substances necessary to the malignant cells due to exhaustion of the host by the overwhelming infection, studies were undertaken to avoid this complication. In a series of experiments it was reported that heat killed *S. cruzi* suspended in plasma or saline exhibited a marked inhibitory and lytic effect on the experimental tumor without producing histologically recognizable damage to normal structures.

The experimental observations of Roskin have been supported by Malisoff who reported that "whole culture lysates" of

Trypanosoma cruzi had regressive effects on experimental tumors.²² However, Hauschka and his associates,²³⁻²⁶ using eight strains of *T. cruzi* including those employed by Roskin and Malisoff, could demonstrate no significant retardation of the growth of five experimental malignant neoplasms. The carefully controlled and exhaustive study of these investigators constitutes formidable evidence against the existence of a carcinoclastic endotoxin in *T. cruzi*.

Cohen et al. have studied the effects of a variety of microorganisms, including three strains of *T. cruzi*, on the growth of tumor cells *in vitro* with negative results.²⁷

Mechanism of Action. The mechanism of the production of hemorrhage and necrosis in various neoplasms by a variety of bacterial filtrates is not altogether clear. In order to understand the experimental evidence which has been gathered on this point it is necessary to review briefly two reactions of hypersensitivity, the Arthus phenomenon and the Schwartzman-Hanger phenomenon.

In 1903 Arthus²⁸ published the results of experiments on rabbits which had received repeated parenteral injections of ordinarily non-toxic foreign protein. When after a variable period ranging from ten days to months or even years a subcutaneous injection of the same foreign protein was given, there followed hemorrhage, edema and finally, in the course of about two days, necrosis with the formation of a sterile abscess at the site of injection. Subsequently, it has been demonstrated that any organ or tissue of a sensitized animal if brought into contact with the specific antigen will exhibit a violent inflammatory response. There is ample evidence that the Arthus phenomenon is an expression of local anaphylaxis, that is, the response to the local reaction of antigen and tissue antibody.²⁹

Schwartzman and Hanger working independently published almost simultaneously the results of experiments on local skin reactivity elicited in a different fashion.^{30,31} They observed that when certain bacterial

filtrates (chiefly culture filtrates of gram-negative organisms) were injected into the skin of normal rabbits, and this was followed in from four to forty-eight hours by an intravenous injection of the same or different filtrates, an intense skin reaction occurred at the site of the original skin injection. The local site at first became hemorrhagic and in a majority of cases necrosis followed. The mechanism of local tissue reactivity to bacterial filtrates cannot be stated with precision. Evidence has been gathered to show that it is not due to local blockade of reticulo-endothelial cells and is not due to inflammation or to increased capillary permeability.³² It therefore becomes necessary to assume that the reactivity is due to some functional disturbance in the cells induced by a variety of, but not all, bacterial filtrates. Further, the injury can be inflicted on the reactive cells only when the provocative material is present in the general circulation.

There are several striking differences between the Schwartzman-Hanger phenomenon of local tissue reactivity and the Arthus phenomenon of local anaphylaxis: In the former the incubation period necessary to elicit the local skin reactivity is about twelve hours and no response can be produced if the local and intravenous injections are separated by more than forty-eight hours, whereas the incubation period for local anaphylaxis is about ten days and sensitivity lasts for months or years. Also the Arthus phenomenon is highly specific in that the antigen used to sensitize the animal must also be used to elicit the response; in contradistinction, culture filtrates of unrelated organisms can serve in demonstration of the Schwartzman-Hanger phenomenon. Whereas any antigenic substance can elicit local anaphylaxis, the local skin reaction can be produced only by certain bacterial filtrates. Finally, the Schwartzman-Hanger phenomenon cannot be transferred passively.

From the foregoing discussion it is immediately apparent that the hemorrhage and necrosis occurring in malignant tumors

following intravenous administration of an appropriate bacterial filtrate is not related to local anaphylaxis, inasmuch as there is no evidence to indicate that the various bacterial toxins are identical with any potentially antigenic constituent of neoplastic cells.

The relationship of the toxin-induced tumor reaction and the Schwartzman-Hanger phenomenon would appear to be close and yet there may be some fundamental differences. In this latter connection it is to be noted that hemorrhage and necrosis in tumors may be induced by intravenous or intraperitoneal injection of a bacterial filtrate without preliminary introduction of the material locally. This apparent fundamental difference in the two phenomena was investigated by Duran-Reynals³³ who explored the possibility that the tumors had been appropriately sensitized due to secondary bacterial infections in tumor-bearing animals. He found, however, that tumors without previous bacterial infection reacted strongly to the effect of active bacterial filtrates. Gratia and Linz assumed that the state of reactivity of tumors was related to the hypothetical virus inducing tumor formation. This is difficult to accept inasmuch as no virus has been identified in tumors in which one obtains the reaction. In addition the Shope papilloma, which is apparently produced by a virus, remains totally resistant to the effects of the active bacterial principles. Further conclusive evidence against this hypothesis is afforded by the fact that tumors induced by local application of carcinogens are susceptible to the bacterial filtrate reaction. The possibility has been considered that rapidly proliferating blood vessels of neoplasms are more susceptible to the injurious effects of bacterial substances than the blood vessels of normal tissue. Support of this hypothesis is provided by the fact that the active principles of bacterial filtrates which elicit the dramatic effect on tumors produce no demonstrable effect upon the blood vessels and tissues remote from the tumor.³⁴ However, it is difficult to explain why such

strong capillary poisons as gold chloride³⁴ or histamine³⁵ fail to affect the neoplasm while in the same animal their characteristic action on normal capillary beds is demonstrable. Also various granulomas, teratomas and all benign neoplasms which may have rapidly proliferating vascular channels are totally resistant to the active principles.^{33,36}

It must be concluded that the tumor reaction and local skin reaction of Shwartzman and Hanger are related to the inherent toxicity of active principles contained within or obtained from bacterial filtrates. There are obvious differences between the two reactions but the fact that there is a definite correlation between the ability of a filtrate of a given micro-organism to elicit the phenomenon of local tissue reactivity in rabbits and the inhibiting effect of this same filtrate upon experimental tumors¹⁴ argues for closely related mechanisms.

Clinical Application. The extensive experimental investigation of the tumor-inhibiting action of bacterial filtrates stemmed from the clinical observation of Busch³ as has already been mentioned. The major advocate of this form of therapy was Coley, who started treating malignancy in this way in 1891 and was still reporting the results of therapy at the time of his death in 1935.^{37,38} The published clinical evidence on the use of bacterial filtrates has recently been compiled³⁹ from the time that Coley utilized the mixed toxins from "*S. erysipelas*" and *B. prodigiosus* until the introduction of the highly purified and potent polysaccharide obtained from culture filtrates of *S. marcescens* by Shear. It is difficult to assess with any confidence the significance of toxin therapy in the reported results because in a large proportion of the cases therapy with toxin was combined with surgery or x-radiation.

Although we are unable to evaluate toxin therapy satisfactorily during the period from 1892 to 1935, we can inquire why it was not more popular and why since 1942 no commercial preparation of bacterial toxins has been available. Seven years after

Coley instituted toxin therapy with a mixed filtrate of "*S. erysipelas*" and *B. prodigiosus* (*Serratia marcescens*), a toxin product from the same organisms was commercially prepared. On the basis of clinical observation Coley was convinced that the commercial preparation was far less potent than the mixed toxins which he had been using. Coley and a few other clinicians used a more stable and more potent preparation made by Tracy.⁴⁰ However, the majority of physicians who attempted chemotherapy of malignancy with "Coley's fluid" had only relatively impotent commercial preparations available. It would therefore appear that one factor to account for the discontinuance of bacterial filtrate therapy was the high variability in the potency of the therapeutic agent. Also since the experimental evidence on the inhibition of tumors by bacterial filtrates was scanty, the importance of bringing the toxin into contact with the neoplasm via the general circulation was not appreciated. Even the chief advocate of toxin therapy, Coley, administered the mixed toxins either into the tumors directly or intramuscularly. Finally, an important deterrent to the general acceptance of toxin was the marked systemic reaction which occurred in most patients treated. This consisted of a chill followed by a temperature elevation of 102° to 104°F. The fever persisted from twenty-four hours to four days. According to the description of Fowler,⁴¹ when hemorrhage and necrosis occurred in neoplasms with extensive distribution there was evidence of hemolysis in the general circulation, presumably as a result of absorption of toxic products of tumor breakdown.

More recently Brues and Shear reported on the toxic reactions to bacterial filtrates.⁴² Using the highly purified and potent tumor-inhibiting polysaccharide from *S. marcescens*, these investigators treated (by intramuscular injections) four patients with advanced malignancies (prostatic carcinoma, lymphosarcoma, multiple myeloma and Ewing's sarcoma). All of these patients died with tumors. Two patients showed

noteworthy relief of symptoms; two patients showed evidence of hemorrhage in tumors at necropsy although it was not possible to decide whether this finding was related to treatment. The patient with multiple myeloma showed no evidence of any effect of this agent on the course of the disease. More significant than the fact that therapy was disappointing were the toxic manifestations induced by the drug. In all instances there was an initial chill followed by fever as high as 107°F. A prolonged period of hypotension occurred, sometimes with anuria and cardiac decompensation. There was an elevation in the blood uric acid and increased uric acid excretion in two patients which was considered to be suggestive evidence of tissue breakdown. It is of interest that the chemical evidence of possible rapid breakdown of nitrogenous substances occurred in the two patients who also had symptomatic relief from therapy. Holloman⁴³ and Oakey⁴⁴ have extended the clinical observations on the effect of the polysaccharide from *S. marcescens*. Their studies differed from those of Shear and Brues in that the polysaccharide was injected intravenously. Essentially the same manifestations were observed following intravenous injection of the polysaccharide as after intramuscular injection. These included hyperpyrexia to as high as 108.4°F., hypotension to shock levels, leukocytosis and frequently pain in the region of the tumor. The hypotension was apparently due to vasodilation and was best controlled by administration of epinephrine.

Included in the seventeen patients treated by Holloman and Oakey were cases of sarcoma (of both soft tissue and bone), malignant lymphoma (Hodgkin's disease and lymphosarcoma), malignant melanoma and leukemia. In a number of instances serial biopsies were taken, and these disclosed intratumor hemorrhage in every instance. Although multiple injections of polysaccharide were employed in several of the patients, none of them was followed sufficiently to evaluate the efficacy of therapy, the primary objective of the in-

vestigation being to study the toxicity of the drug.

At the present time there is inadequate information available on the application of *S. cruzi* endotoxin in the therapy of human neoplastic disease. Klyueva⁴⁵ recently briefly summarized the results of treatment in nineteen patients with carcinoma of the larynx, carcinoma of the cervix, carcinoma of the breast and carcinoma of the lip. Injections of the endotoxin, which is called KR (Klyueva-Roskin), by the subcutaneous, intramuscular or intratumor route were followed by pain at the site of the malignancy. After a variable period of time there was disintegration of the neoplasm with localized suppuration. Since the author does not provide details of the follow-up, it is impossible to evaluate the results objectively. Klyueva reports a favorable response in the majority of patients.

Comment. The foregoing comments indicate the extensive investigations which have been carried out on the effects of microbial products on neoplastic disease. From the experimental observations there can be no doubt that profound alterations of malignant cells may be induced by these products. It is clear that their application in human neoplastic disease for the present is hazardous and of doubtful efficacy. The preparations which have been used are still in a relatively crude state, however, and it is possible that further fractionation and precise chemical characterization will lead to elimination of the components which produce toxic reactions and also to further concentration of the active carcinolytic principles.

ANTIRETICULAR CYTOTOXIC SERUM

Background and Rationale. The significant contribution of the reticulo-endothelial system in cellular and humoral immunity is well established. There are also other physiologic mechanisms in which this system participates. These include (1) erythrocyte phagocytosis and the metabolism of hemoglobin and bile; (2) repair and regeneration of tissues and (3) lipid storage

metabolism. Of particular interest in connection with this discussion is the evidence for the part played by the reticulo-endothelial system in limiting neoplastic growth.

There are at least two types of study which circumstantially implicate the reticulo-endothelial system as an important deterrent to neoplastic growth and development.⁴⁶ Morphologic examination of this widespread system in experimental tumor-bearing animals has revealed a marked hypertrophy under certain circumstances, particularly of the elements in the liver and spleen. This is manifested by proliferation of histiocytes and Kupffer cells in the liver and by reticular hyperplasia of the spleen. It would also appear significant that a correlation exists between the reaction of the follicular elements of the spleen in animals treated with chemical carcinogens and the incidence of tumor production in these animals. In refractory animals there is marked hyperplasia of follicles and of reticulo-endothelial elements whereas in those animals in which a malignancy is produced follicular aplasia of the spleen is noted.⁴⁷ In addition to these histologic findings the gross anatomy of the spleen has been found to be abnormal inasmuch as hypertrophy resulting in an increased weight of the organ has regularly been observed in animals bearing various types of neoplasms.⁴⁸⁻⁵⁰ It has been further demonstrated that splenic hypertrophy can also be induced in animals by means of injections of blood derived from animals or humans with malignancy.⁵¹ Recently this has been employed as a diagnostic test.⁵² Splenic hypertrophy in experimental animals with tumors is interpreted as an expression of a physiologic defense mechanism. It is noteworthy in this regard that malignant tumors rarely metastasize to the spleen, a fact which is striking in view of the rich supply of blood and lymph vessels to this organ and its anatomic proximity to gastrointestinal organs which are so frequently affected by malignancy. In a survey of 580 autopsies of cancer patients only 3.2 per cent showed splenic metastases.⁵³

When the function of the reticulo-endothelial system is depressed, either by splenectomy or by functional impairment of the elements caused by loading them excessively with certain colloids, there appears to be stimulation of tumor development and growth. Thus, Andervont⁵⁴ demonstrated that when mouse tumors were grafted to mice of another strain they grew far better and faster if the recipients had previously been injected with trypan blue. Similar observations have been made with chemically induced tumors; the development and growth of tumors due to coal tar or dibenzanthracene were found to be accelerated and increased in splenectomized mice as compared with the response in control animals.⁵⁵

However, it is impossible to accept without question the hypothesis that the cells of the reticulo-endothelial system elaborate some principle which possesses growth-inhibitory and/or lytic properties for neoplastic cells. It is, for example, difficult to reconcile with the alleged carcinoclastic activity of the reticulo-endothelial system the characteristic infiltration of lymph nodes, liver and spleen by the malignant lymphomas. Also it has been demonstrated that tumors and spleen can be cultivated in the same tissue culture medium without significant depression of the growth rate or characteristics of either tissue.^{56,57}

Historically, the development of antireticular cytotoxic serum stems from the teaching of Metchnikoff which emphasized the pharmacologic principle that small doses of a toxic drug may stimulate cell functions rather than depress them. Metchnikoff reasoned that it should be possible to stimulate the function of a tissue by administration of small doses of antiserum specific for the tissue. Parenthetically, it is to be noted that in the light of present day knowledge of mechanisms of drug action the pharmacologic principle enunciated by Metchnikoff is increasingly difficult to defend. Bogolomets, a student of Metchnikoff, postulated that because of the pervasiveness of the reticulo-endothelial system

and the multiplicity of its functions, the functional state of this system was a major determinant of health and of resistance to infection and degenerative disease. He further believed that the functional capacity of the physiologic system in man could be improved by administration of small or stimulating doses of a cytotoxic serum produced in animals by injection of antigens prepared from organs rich in reticulo-endothelial tissue. He prepared such a serum for human use by inoculating horses with the cells of spleen and bone marrow from human cadavers. The experimental observations and clinical applications of antireticular cytotoxic serum were carried out exclusively in the U.S.S.R. until very recently. These have been summarized in detail by Bogolomets⁵⁸ and Straus.⁵⁹ Suffice it to say that at a conference held in Russia in 1942, at which time 2,500 clinical observations were surveyed, it was concluded that the therapeutic effect of ACS was clearly established in war traumatism and in the following diseases: (1) frostbite and wounds, especially slowly knitting bone fractures and indolent, infected wounds; (2) infectious diseases, especially typhus; (3) diseases of the nervous system, especially traumatic and infectious diseases; (4) diseases connected with disordered trophic functions of tissue, especially peptic ulcers.

Fedyushin and Bogolomets demonstrated that small doses of ACS significantly decreased the number of "takes" of transplanted cancer, caused the disappearance of large cancers already present and reduced the number of metastases in mice.⁶⁰

The claims for antireticular cytotoxic serum have been investigated experimentally in this country by Straus and his colleagues.^{61,62} On the basis of enthusiastic statements of a number of Russian investigators regarding the favorable effects of small doses of ACS on the rate and extent of healing of fractures, these authors carried out a series of observations on experimental fractures in the rabbit. ACS was prepared in rabbits and goats using human spleen and bone marrow for the

antigen. The titer of ACS was determined by a complement fixation technic described by Marchuk.⁶³ In 156 rabbits with experimental fractures the authors investigated the effects of stimulating doses of ACS (0.00125 ml., titer 1:320) and depressing doses of the same serum (0.1 ml.) on (1) x-ray changes of the healing fracture sites, (2) gross and microscopic alterations of the bones and (3) breaking strength of the healed fractures. Although there were no apparent differences in the first two criteria just mentioned, statistical evaluation of the breaking strength of the healed fractures indicated highly significant differences between each of the groups and its control.

From these results the authors conclude that "stimulation of the healing of experimentally produced fractures in rabbits was induced with small (stimulating) doses of antireticular cytotoxic serum and depression of healing followed large (depressing) doses as claimed by the Soviet investigators."

Mechanism of Action. The mechanism of action is completely unknown. The experimental observations discussed in the foregoing section (which have not been confirmed) would indicate that there is a lack of specificity of the action of ACS inasmuch as human antigen was employed to produce the antibodies and these presumably stimulated or depressed the rabbit reticulo-endothelial system.

Clinical Application. Use of antireticular cytotoxic serum in the therapy of malignant disease has been reported only in summary form by the Russian investigators.⁵⁸ In this country Davis⁶⁴ has made a preliminary but unpromising report on his experience with the material in a variety of neoplasms and Friedman and Stritzler reported a negative result in mycosis fungoides.⁶⁵ Skapier⁶⁶ has treated twenty-two cases of Hodgkin's disease. There was no evidence that a fundamental effect on the neoplasm was produced although transient weight gain and decrease in the erythrocyte sedimentation rate was noted. Because of the paucity of objective data, it is impossible at this time to assess the contribution if any

to the chemotherapy of cancer made by this approach. Rogoff and his associates⁶⁷ attempted without success to confirm Russian claims of striking benefit of ACS in arthritis.

Comment. Antireticular cytotoxic serum has been presented in detail primarily as an example of many investigations which stem from the hypothesis that the reticulo-endothelial system is a significant barrier to the development and/or spread of malignant disease in man. This hypothesis, which lacks convincing proof, has been repeatedly advanced to provide the rationale for the therapy of malignant disease with organ extracts. The most recent report of this nature is that of Watson, Diller and Ludwick⁶⁸ who advance inconclusive evidence that an extract of calf spleen alters the course of human malignancy. Another example of a chemotherapeutic agent stemming from the same hypothesis is teropterin which is to be discussed in the next section.

FOLIC ACID CONJUGATES

Background and Rationale. Lewisohn and his associates have devoted their research efforts over a period of years to the therapy of transplanted and spontaneous tumors in mice. In 1938 they reported that an extract of beef spleen caused regression in a significant number of instances of sarcoma 180.⁶⁹ An extract of mouse spleen was found to have a cytotoxic effect on spontaneous breast carcinoma in mice. Due to the impracticality of large scale extraction of mouse spleens, extracts obtained from a number of other sources were screened for their antitumor activity. The attention of this group of investigators was focused on the components of vitamin B complex by their observation that extracts of barley and brewers' yeast seemed to cause regression of spontaneous mammary adenocarcinoma in mice.⁷⁰ In 1945 the Leuchtenbergers, Lazlo and Lewisohn^{71,72} reported that *L. casei* fermentation factor caused complete regression of 30 per cent of spontaneous breast cancers in three different strains of mice treated with daily intravenous injections of

5 micrograms of the material. At the time of their report this was considered to be pteroylglutamic acid, i.e., folic acid. Subsequent chemical characterization of the *L. casei* fermentation factor showed this to be a folic acid conjugate, pteroyl triglutamic acid. Folic acid was ineffective.⁷³

The results of the experimental chemotherapy of Lewisohn and his co-workers could not be confirmed by Sugiura,⁷⁴ Burk⁷⁵ and Morris.⁷⁶

Mechanism of Action. No mechanism of action has been suggested.

Clinical Application. Farber and his associates published a preliminary report on the use of pteroyl glutamic acid conjugates in malignant disease in man.⁷⁷ Their series of patients treated with teropterin and diopterin (pteroyldiglutamic acid) includes acute leukemia; astrocytoma; Ewing's tumor; carcinoma of the rectum, colon, stomach, cervix, prostate, pancreas, esophagus, bladder, breast, gallbladder, kidney and ovary; Hodgkin's disease, lymphosarcoma; osteogenic sarcoma; ependymoma; leiomyosarcoma of the stomach; spongioblastoma multiforme; seminoma; hypernephroma; chondrosarcoma; epidermoid carcinoma of the pharynx and of the tongue and embryoma of the kidney. The authors stated that, in general, the patients experienced "improvement in energy, appetite and sense of well being." Since no details of the cases were presented, it is impossible to evaluate the effect of therapy in their patients. It is noteworthy that in eleven patients from whom serial biopsies were obtained before, during and after teropterin therapy there was "no change in the tissues which could be regarded as a deleterious effect of the substance employed." The authors conclude that the drug is non-toxic and since there were instances of improvement which seemed to be greater than could be accounted for by the concomitant conventional therapy (such as radiotherapy), they suggest further clinical trial.

Additional evidence on the efficacy of teropterin in human neoplastic disease was presented by Klainer,⁷⁸ Lehv and his co-

workers⁷⁹ and Meyer⁸⁰ at a recent symposium devoted to the effect of derivatives of folic acid on certain types of neoplastic disease. Although more details of the subjects treated were given in these latter reports, only a limited number of patients were studied for short periods of time. For the most part the patients were receiving other forms of therapy at the same time that teropterin was being employed which makes it difficult to evaluate the contribution of the drug in question. There was no objective evidence recorded which indicated that the course of the neoplastic diseases studied had been significantly altered.

Comment. This brief summary of the current status of pteroyl triglutamic acid in the chemotherapy of malignant disease was included only because teropterin has recently received considerable publicity in the lay press as a significant contribution to this serious problem.

It has been demonstrated that man is well equipped with enzymes, so-called conjugases, which efficiently split folic acid conjugates with the release of folic acid.⁸¹ Administration of pteroyl triglutamic acid parenterally therefore presumably results in the removal of two glutamic acid molecules *in vivo*, leaving folic acid. This vitamin has been shown to play a significant role in the maturation of cells of the hemopoietic system. Since there is no evidence that malignant disease is an expression of a folic acid deficiency, there is no apparent rationale for teropterin therapy.

The only experimental evidence that teropterin has a cytotoxic action on malignant cells is the unconfirmed work of Lewisohn and his associates. Woll⁸² and Little et al.⁸³ have shown that the growth of the Rous chicken sarcoma is actually stimulated by folic acid and inhibited by folic acid antagonists.

At the present time there is no evidence from the reported clinical trials with teropterin that this drug affects human neoplastic growth or significantly alters the course of malignant disease in man. The Council on Pharmacy and Chemistry of the American

Medical Association reached the same conclusion on the basis of reports which it received on the results of teropterin and diopterin therapy in 275 patients.⁸⁴

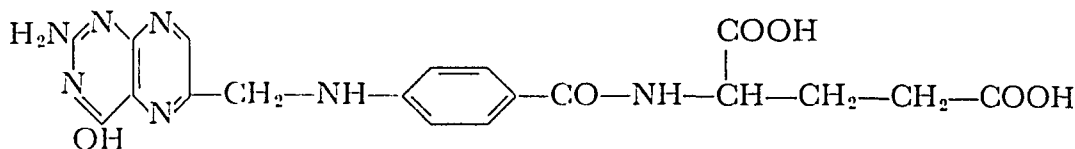
However, the Council noted that relief of pain and subjective improvement was reported in 50 per cent of the patients. It was considered possible that this analgesic action, particularly of teropterin, might offer a significant advantage over the narcotics because of the absence of side reactions, addiction and hypnotic effects. Inasmuch as the psychotherapeutic factor associated with the use of a new form of therapy was not controlled in these studies, it is not permissible to accept the alleged analgesic action of the folic acid conjugates as a fact. In the absence of either conclusive experimental or clinical demonstration that these compounds have any fundamental influence on malignant disease the authors believe that the implications in the lay press and in the advertising to the medical profession are unfortunate, misleading and unwarranted.

FOLIC ACID ANALOGS

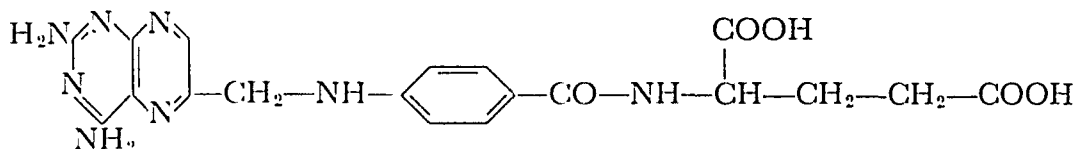
Background and Rationale. The development of metabolic antagonists in the form of chemical analogs of essential metabolites has provided significant research tools for the classification of a variety of physiologic cellular mechanisms.⁸⁵ As each new member of the vitamin B complex has been chemically characterized one or more chemical analogs has been synthesized. Numerous analogs of pteroylglutamic acid have been prepared and a number of them have been found to be potent folic acid antagonists as indicated by their ability to prevent the growth of *Str. faecalis* R when added to culture media rich in folic acid.^{86,87} The two types of analogs which are pertinent to this paper are those in which the substituents of the pteridine ring of folic acid are either changed or other groups added, and those in which besides these alterations the glutamic acid is substituted by another amino acid. The chemical relationship of the analogs to folic acid can

best be illustrated by the structural formulas of the drugs which are currently receiving extensive clinical trial in cancer chemotherapy.

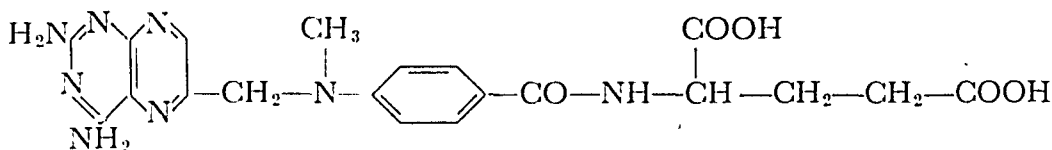
by feeding diets high in pteroylglutamic acid.^{82,83} However, these latter observations cannot be accepted as evidence that neo-



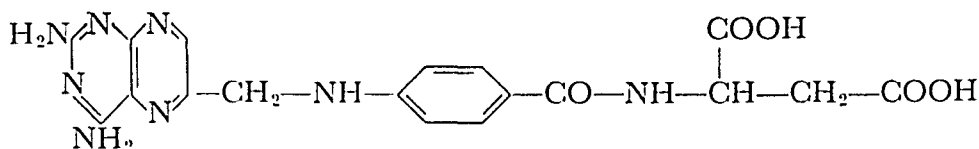
Pteroylglutamic acid (folic acid)



4-amino-pteroylglutamic acid (aminopterin)



4-amino-N¹⁰ methyl-pteroylglutamic acid (α -methopterin)



4-amino-pteroylaspartic acid (amino-an-fol)

In the clinical trials with the folic acid conjugates Farber and his associates noted that the course of the disease in patients with acute leukemia appeared to be accelerated. The apparent stimulation of abnormal leukocyte production in the bone marrow led him to the hypothesis that folic acid was an essential metabolite for leukopoiesis. On the basis of these observations he instituted clinical trials with folic acid antagonists in acute leukemia.

Mechanism of Action. As has been mentioned in the preceding sections it has been demonstrated that the folic acid analogs act as antagonists in certain biologic systems. This can be shown clearly in the case of certain bacteria (*S. faecalis* R) which require folic acid for their growth. It has also been shown that the growth rate of the Rous chicken sarcoma can be significantly depressed by administration of folic acid analogs to the host and can be accelerated

plastic cells are dependent upon folic acid for it is known that this tumor is caused by a filterable virus. The mechanism of action of the folic acid analogs in human neoplastic disease is not known, but as will be seen in the succeeding section circumstantial evidence indicates that it is unrelated to folic acid antagonism.

Clinical Application. Farber, Diamond et al.⁸⁸ have made a preliminary report on the immediate results of treatment with aminopterin in sixteen cases of acute leukemia in children. In ten of these patients clinical and hematologic remissions occurred during therapy with the folic acid analog for intervals ranging from two weeks to six months. The remaining six were either unimproved or made worse. Careful analysis of these cases by the Boston group has led them to the conclusion that the remissions have not been correlated with either blood transfusions or infection which are important

factors associated with spontaneous remissions. The remissions have been characterized by decrease in the blasts and other immature leukocytes in both the peripheral blood and the bone marrow. Decrease in the size of subcutaneous lymph nodes and of hepatosplenomegaly also occurred and is indicative of a cytotoxic effect on leukemic infiltrations. With the onset of remission, there has also been an increase in the erythrocytes and platelets. In subsequent reports Farber stated⁸⁹ that in a much larger series "about 52 per cent" of the cases of acute leukemia in children have shown hematological and/or clinical improvement which can be classed as a remission. These patients have received α -methopterin, amino an-fol as well as aminopterin.

In the case of aminopterin the drug is administered subcutaneously or intramuscularly at daily intervals in doses of 0.5 mg. to 1.0 mg. Therapy is continued until remission occurs or until toxic manifestations appear. Evidences of toxicity include severe stomatitis, ulceration of the intestinal epithelium, pancytopenia due to bone marrow depression and alopecia. Of these manifestations stomatitis frequently occurs first and it is the signal for immediate discontinuation of the drug; after one to two weeks therapy may be resumed cautiously. Folic acid and liver extracts have been given simultaneously with aminopterin in an attempt to prevent toxicity but this has been unsuccessful.

The results of folic acid analog therapy in acute leukemia in adults have been less impressive although Dameshek⁹⁰ has stated in an editorial that in about one-third of a small series of patients there has been a significant improvement in the clinical and hematologic condition. In all cases thus far reported, including children and adults, the period of follow-up has been too brief to determine whether the course of the disease can be significantly altered by therapy with these chemicals.

It is of interest and significance that cases of Hodgkin's disease, lymphosarcoma and neuroblastoma have had temporary re-

missions following aminopterin therapy.⁸⁹ No detailed reports on the patients are yet available so that it is impossible to compare these results with those obtained by conventional radiotherapy or by nitrogen mustard.

Comment. It is too early to assess the significance of the folic acid analogs in cancer chemotherapy. Because of the limited understanding of the fundamental biology of acute leukemia, it is difficult to evaluate the practical importance of temporary hematologic remissions. If with further clinical experience it is demonstrated that the life expectancy of patients with acute leukemia is increased, a very significant advance in cancer chemotherapy can be claimed. At the present time the severe toxic manifestations which follow use of the folic acid analogs constitute a serious limitation to their general use.

Irrespective of their ultimate importance in clinical therapy, these drugs have great heuristic value. In connection with this the available observations indicate that their mechanism of action in human neoplastic disease is not specifically related to folic acid antagonism. This conclusion rests on the circumstantial evidence that neither the beneficial effect in certain cases of acute leukemia nor the toxic manifestations can be counteracted by simultaneous administration of folic acid.

STILBAMIDINE

Background and Rationale. In visceral leishmaniasis or kala-azar the serum globulin is usually markedly elevated.⁹¹ Following adequate therapy with tervalent or quinquivalent organic antimonial drugs, the signs and symptoms of the disease disappear and the serum globulin level returns to normal. Following the discovery by Yorke⁹² that the diamidines, stilbamidine, pentamidine and propamidine were effective chemotherapeutic agents against a number of experimental protozoal infections, these drugs were found to be active against *Leishmania donovani* infections in man. As with the antimonials, stilbamidine therapy

in human leishmaniasis was followed by a decrease of the elevated plasma globulins.^{91,93}

In multiple myeloma the plasma globulin is frequently increased. On the basis that stilbamidine therapy of kala-azar causes a decrease in plasma globulin Snapper selected this drug for a therapeutic trial in multiple myeloma.^{94,95}

Mechanism of Action. The morphology of myeloma cells secured by sternal marrow aspiration has been intensively studied by Snapper following stilbamidine therapy.^{96,97} After four to six weeks of therapy basophilic granules or inclusion bodies appear in the cytoplasm of the myeloma cells of many patients. In none of the other cellular components of the marrow have such inclusions been found. Utilizing chemical and physical methods, Snapper and his associates characterized the chemical composition of the myeloma cell inclusion bodies. From a combination of specialized staining technics before and after exposure of the myeloma cells to ribonuclease it was concluded that the inclusion bodies contained ribose nucleic acid. This conclusion was confirmed by ultraviolet microscopy, in that the granules were found to have an ultraviolet absorption (2600Å) which was identical with that of ribose nucleic acid. This observation takes on added significance when correlated with the results of *in vitro* experiments by Kopac.⁹⁸ This author demonstrated that stilbamidine in high dilutions dissociates protamine ribonucleate with the release of protamines from these compounds. Stilbamidine reacts with nucleoproteins *in vitro*, an insoluble stilbamidine-ribose nucleate complex being formed. Kopac concluded that the cytotoxic effect of stilbamidine in experimental tumors^{99,100} could be due to the fact that this diamidine dissociates nucleoproteins which are essential to neoplastic cells or that the nucleoproteins of neoplastic cells are more readily dissociated by stilbamidine than are those present in normal cells.

Thus, it is possible that the granules appearing in multiple myeloma cells following stilbamidine therapy are, in fact, stilbami-

dine-ribose nucleate complexes. In this connection it has been demonstrated that stilbamidine does localize in myeloma tissue.⁹⁷

Clinical Application. Although stilbamidine has been given a therapeutic trial in a variety of neoplastic diseases, including lymphatic and myeloid leukemia, lymphosarcoma, Hodgkin's disease and various carcinomas, it has been found effective only in multiple myeloma.⁹⁵ Snapper¹⁰¹ has reported on the results of therapy in thirty-five patients in whom the diagnosis was documented by sternal marrow biopsies. The one symptom common to all of the patients was excruciating pain which caused the majority of them to be bedridden. In 80 per cent of the cases the bone pain was either completely or partially relieved by therapy. Although the period of follow-up is too brief to assess the effect of stilbamidine treatment on life expectancy, it is apparent from Snapper's observations that the disease is halted only temporarily at best.

It was noted that in spite of evident clinical improvement in most of the cases the myeloma cells or myeloma cells with basophilic granules in the cytoplasm persisted. In addition Bence-Jones proteinuria continued and the hyperglobulinemia was not affected. Serial x-ray examinations of the skeleton did not disclose recalcification of the bone lesions, but neither was there roentgenographic evidence of progression of the disease.

During a course of stilbamidine therapy for multiple myeloma it is important that the patient be maintained on a low animal protein diet. When a normal diet is permitted, therapy is uniformly unsatisfactory.^{94,95,101} The explanation for this dietary regimen is not clear, nor is there a report of the effect on myeloma bone pain of a restricted animal protein diet alone.

Stilbamidine freshly dissolved in isotonic saline is administered intravenously preferably, or intramuscularly if the subcutaneous veins are inadequate. It is irritating by intramuscular injection and it is recommended that 2 per cent procaine be added

when administration is by this route. The daily dosage suggested is 150 mg. in a single administration; the total therapeutic dose is between 3,000 mg. and 6,000 mg.

Toxic reactions to stilbamidine may be immediate or delayed. The immediate toxicity is manifested by local pain along the course of the vein, a feeling of warmth in the face and a drop in blood pressure which may be great enough to lead to syncope. This latter reaction is due to marked peripheral vasodilatation as a result of the direct relaxing effect of the drug on the smooth muscle of the arterioles. This reaction can be prevented by administration of epinephrine just before the stilbamidine injection, or the stilbamidine can be slowly injected into the rubber tubing of an intravenous saline infusion.

When stilbamidine was first used in the therapy of leishmaniasis, delayed toxic effects on the liver, kidney and nervous system were noted. It was soon determined that these were not due to stilbamidine but to a degradation product which appeared when stilbamidine in solution was exposed to light.¹⁰² Arai and Snapper¹⁰³ have recently reported the results of careful studies of liver and kidney function following stilbamidine therapy in twenty-six patients and no significant changes were noted. The prevention of parenchymal necrosis is probably due to the fact that at the present time freshly prepared solutions of stilbamidine are used exclusively. These authors also found no significant changes in the formed elements of the peripheral blood.

A toxic reaction which has not been prevented by use of fresh solutions of stilbamidine is subjective disturbances and dissociated anesthesia of areas supplied by the sensory branches of the trigeminal nerve, which may develop two and one-half to five months after the completion of stilbamidine therapy.¹⁰⁴⁻¹⁰⁶ The reaction is characterized by subjective symptoms of numbness, formication, heaviness and itching of the affected areas. The sensation of light touch is lost but pain, temperature

and pressure modalities are intact. From experimental studies it appears probable that the symptoms and signs are due to toxic degeneration of the principal sensory nucleus of the fifth nerve. In stilbamidine intoxication in dogs neuronal and myelin disintegration have been observed in this area.¹⁰⁷ In Arai and Snapper's series of stilbamidine treated patients eighteen were followed for a sufficient time to evaluate the incidence of this reaction. It occurred in ten of the eighteen patients. The symptoms persisted over a protracted period and then spontaneously gradually diminished in intensity. No satisfactory therapy of this toxic manifestation was found.

Comment. The rationale for the use of stilbamidine and more recently antimonials¹⁰⁸ in the chemotherapy of multiple myeloma has been presented. The hypothesis rests on the assumption that the hyperglobulinemias of kala-azar and multiple myeloma are similar. We believe that use of these drugs is empiric, however, in view of the following established facts:

First, the therapeutic response of patients with kala-azar treated with stilbamidine or antimony salts is dependent on the toxic action these compounds exert on the parasite causing the disease rather than by altering serum protein synthesis. In multiple myeloma no causative organism has been implicated.

Second, careful studies on the serum of patients with kala-azar¹⁰⁹ and with multiple myeloma¹¹⁰ have revealed certain fundamental differences in the serum proteins in these two conditions. An elevation of the euglobulin and pseudoglobulin γ fractions (Howe) with normal pseudoglobulin π is commonly seen in kala-azar. In multiple myeloma, hyperproteinemia with a similar distribution of Howe and electrophoretic fractions may occur; but the studies of Gutman and his co-workers^{110,111} in a series of forty-three myeloma patients indicate that in many cases Bence-Jones proteins and other abnormal protein components appear in the serum in significant concentration. Such components can, by special

technics, be readily differentiated from the γ -globulins composing the serum globulin increment in kala-azar and have an altogether different significance. Bence-Jones proteins presumably are formed by the myeloma cells and the apparent persistence of Bence-Jones proteinemia following stilbamidine therapy would seem to be significant.

Although these data lead to the conviction that the rationale proposed by Snapper for use of stilbamidine in multiple myeloma is without basis, the drug may, of course, be used empirically. Since there is ample evidence that the fundamental lesions are not significantly altered and that the abnormal serum protein patterns persist unchanged following therapy, it must be concluded that the drug merely provides symptomatic relief. In view of this and the high incidence of drug toxicity on the trigeminal nerve and the protracted duration of therapy we believe that stilbamidine therapy of multiple myeloma should be used only as a last therapeutic resort.

URETHANE

Background and Rationale. Use of urethane as a chemotherapeutic agent in malignant diseases stems from the experimental observations of Haddow and Sexton on the effect of the drug on animal tumors.¹¹² These investigators systematically examined the effects on the growth of experimental tumors of those drugs which had in the past been reported to have effects upon mitosis. They examined phenylurethane and its derivatives with particular care because botanists and plant physiologists had repeatedly noted the striking arrest of mitosis in the cells of the roots of cereals and other plant species. In fact, so marked was this action that Templeman and Sexton suggested use of isopropyl phenylcarbamate as a "weedicide." Although ethylcarbamate (urethane) had been found inactive against plant growth, it was not neglected by Haddow and Sexton in their screening program for carcinolytic agents. The experimental neoplasms utilized in these studies were a

spontaneous mammary adenocarcinoma in mice and the Walker rat carcinoma. Several of the carbamic acid esters were found to retard growth of these tumors, urethane being the most active. In mammary carcinoma progress of the tumor was inhibited only during administration of the drug, whereas in the experiments on the Walker carcinoma a profound modification in histologic structure was produced, characterized by an apparent maturation of the undifferentiated cells. It is to be noted that death of the malignant cells was not a prominent effect of the drug on the tumor. The authors state, "Although the growth effects above described were in no way dramatic, their reproducibility, and the interest of the circumstance that they might be brought about by a known substance as simple and as readily available as urethane, suggested the advisability of testing its action in advanced and inoperable or otherwise intractable cancer in the human subject."

Mechanism of Action. The mechanism of action is unknown. It would not be justified, however, to omit mention of several possible mechanisms which have been suggested. Because urethane was widely employed in Europe as an anesthetic agent in laboratory experiments, a considerable body of information is available on the mechanisms of narcosis produced by this drug. It has been demonstrated that urethane is able to suppress nuclear and cell division of the sea urchin egg without causing an accompanying reduction of oxygen consumption.¹¹³ This observation indicates that the drug interferes with intracellular enzyme systems which are not directly related to respiration. Experiments on brain tissue¹¹⁴ and on bacteria¹¹⁵ in general confirm this finding, but the specific catalytic substances whose functions are depressed are not known.

In addition to the possibility that urethane affects cell growth by the same mechanism involved in its production of narcosis Haddow and Sexton suggest that the drug might act by competing with a natural amine involved in the biosynthesis

of nucleotides. This concept is based on the isotope studies of Plentl and Schoenheimer¹¹⁶ which indicated that the synthesis of nucleoproteins was not accomplished by utilization of relatively complex building blocks such as purines or pyrimidines but rather from smaller molecules such as certain amino acids. As yet there is no direct evidence for this attractive hypothesis of competition.

Clinical Application. The clinical investigation of urethane in man was initiated in 1943 by Paterson and her associates.¹¹⁷ The first patients treated had far advanced malignant disease. The clinical results were disappointing; but it was noted that in some instances there was a striking fall in the leukocyte count. This suggested the trial of urethane in patients with leukemia.

Eighteen patients with chronic myelogenous leukemia were treated and at the time of the report the mean observation period was six months. There was one patient with acute myelogenous leukemia in whom the drug had no apparent effect and in whom the course of the disease was unaltered.

Conventional radiotherapy was used in six of the eighteen patients when either a trial on urethane had proved unsuccessful in reducing the count or side reactions to the drug were of such magnitude that it had to be discontinued. The dosage of urethane was, in part, determined by the tolerance of the patient. Most patients received 3 Gm. of the drug per day, but as much as 5 Gm. per day have been given. The amount of urethane necessary to produce a fall in the leukocyte count to about 20,000 per cu. mm., which was the point at which therapy was discontinued, varied within wide limits (19 Gm. to 134 Gm.). This dose could not be correlated either with body weight or with absolute decrease in the number of white cells. Considerable variation existed in the time taken for the leukocyte count to fall to the arbitrary end point of 20,000 per cu. mm. (eleven to thirty-six days, average thirty days). It was noted that immature cells were most sensitive to the

drug, in that the differential white cell examinations revealed a disappearance of the myeloblasts and premyelocytes. The effect on erythropoiesis can be seen in Table 1. The spleen, markedly enlarged in all cases, was reduced after treatment, in some instances until it was no longer palpable.

In nine cases of chronic lymphatic leukemia urethane therapy alone was employed. It was found that the hematologic response to the drug was less satisfactory than in chronic myelogenous leukemia. In general the qualitative changes were similar in the two types of the disease, but the quantitative improvement in signs and symptoms was more variable in the lymphatic blood dyscrasia.

The changes in the total peripheral white count and hemoglobin, together with the clinical evaluation of the results, are summarized in Table 1.

The authors compared the urethane treatment of chronic leukemia with results which they had obtained in the past with x-ray therapy to the spleen. They concluded that the changes induced by chemotherapy and radiotherapy were strikingly similar. No significant differences were noted as regards: (1) quantitative or qualitative alterations produced, (2) duration of therapy required to produce the changes, (3) effect on splenomegaly or (4) improvement of the hemoglobin concentration. A comparison of the length of life of the patients treated by the two methods is not possible at the present time.

The observations of the British workers have been confirmed in both experimental¹¹⁸⁻¹²² and human leukemia.¹²³⁻¹²⁸ There are sufficient data in the reported results of urethane therapy in 108 patients with leukemia to provide an approximate evaluation of the immediate response. In forty patients with acute leukemia urethane therapy did not alter the course of the disease and no significant clinical and/or hematologic remissions were induced; in forty-six cases of chronic myelogenous leukemia the immediate response was satis-

factory in thirty (65 per cent); a satisfactory response has been reported in eleven of twenty-nine patients with chronic lymphatic leukemia (38 per cent).

In Paterson's experience¹¹⁷ no significant remissions were induced in thirteen cases of

from the prostate of castrate dogs given testosterone and urethane simultaneously was not decreased below those values obtained with testosterone administration alone.

Comment. From the available evidence

TABLE I
URETHANE TREATMENT OF CHRONIC LEUKEMIA

	Before Treatment		Two Months after Initiation of Treatment		Six Months after Initiation of Therapy				
	Average Hemo-globin (per cent)	Average White Blood Cells (mm. ³)	Average Hemo-globin (per cent)	Average White Blood Cells (mm. ³)	Average Hemo-globin (per cent)	Average White Blood Cells (mm. ³)	Im-proved	Un-satis-factory	Died
Chronic myeloid leukemia...	52	318,000	68	19,000	74	54,000	7	3	2
Chronic lymphatic leukemia...	56	216,000	78	25,000	64	47,000	2	3	4

Data calculated from Paterson, E., et al.¹¹⁷

advanced carcinoma of the breast or in eleven cases of miscellaneous malignant diseases, including Hodgkin's disease, lymphosarcoma, multiple myeloma, carcinoma of the rectum, malignant mixed salivary tumor or malignant seminoma. In general the observations of others corroborate these findings although it has been suggested that urethane be tried in highly anaplastic, disseminated epitheliomas.¹²⁹

Recently Huggins¹³⁰ reported that the drug had beneficial effects on prostatic cancer with metastases. In one patient who had an advancing prostatic cancer following remission induced by castration, estrogen administration and radiotherapy, 4 Gm. of urethane daily for five days followed by a daily maintenance dose of 1 Gm. for six weeks, eliminated bone pain and caused a marked decrease in the size of the primary tumor. As with androgen control therapy the serum acid phosphatase levels fell after institution of treatment. Huggins demonstrated that the mechanism of action of ethylcarbamate was not through an anti-androgenic effect; the volume of secretion

it may be concluded that urethane is a satisfactory therapeutic agent in producing temporary remission in chronic lymphatic and myelogenous leukemia. Whether the duration of life of leukemia patients so treated will be significantly prolonged is not yet established. On the basis of Huggins' results it would appear that ethylcarbamate may be an additional useful weapon against prostatic carcinoma. It is to be noted that use of the drug is potentially hazardous since it can produce marked depression of bone marrow function.¹³¹

ANDROGEN CONTROL THERAPY
OF MALIGNANCY

Background and Rationale. Alteration of the internal environment by biologic means has dramatically influenced the treatment of inoperable carcinoma of the prostate. At the present time administration of estrogen or bilateral orchiectomy, or both, is an accepted and generally employed program of therapy for this malignancy. The rationale for this type of treatment rests upon sound physiologic observation.

As early as the nineteenth century it was noted that an interrelationship existed between testicular function and the prostate. In 1837 Civiale¹³² described marked regression of the prostate in patients in whom bilateral orchiectomy had been performed incidental to herniorrhaphy. The common practice of orchiectomy for benign hypertrophy of the prostate in the latter part of the nineteenth century rested, in large part, upon the experimental observations of White¹³² who carefully noted the effect of castration on the prostate gland of dogs. From his observations on the atrophy of glandular and muscular elements of the prostate he suggested this operative procedure for benign prostatic hypertrophy in man. By the turn of the century the operation was dropped because of unsatisfactory end results and because surgical technics for prostatectomy had been greatly improved. These early laboratory and clinical experiments demonstrated the dependency of the prostate upon normal testicular function.

Understanding of the effect of the secretion from the male and female gonads on the physiology of the prostate was extended by Huggins and his co-workers who devised a relatively simple operative procedure in dogs whereby the course of urine was deviated and the prostate was isolated from the bladder.¹³³ In such animals it was possible to demonstrate that castration caused complete cessation of prostatic secretion in seven to sixteen days. A similar effect was achieved by administration of estrogens to normal dogs. It was further shown that the ability of estrogen to decrease prostatic secretion and to cause shrinkage of the gland was related to its anti-androgenic action. In a castrate dog to whom androgen in the form of testosterone propionate was administered a normal or greater than normal amount of secretion was elicited and the gland grew. When estrogen was administered simultaneously with the androgen in appropriate dosage, it was possible to abolish the secretion of the gland and to reduce its size markedly. Histologic ex-

amination of the prostate gland in men subjected to orchiectomy for benign hypertrophy demonstrated principally an involution of the prostatic epithelium, with only minimal changes in the smooth muscle or connective tissue.¹³⁴

Physiologic study of the prostate gland and of prostatic malignancy was greatly facilitated by the discovery of Kutscher and Wolbergs that normal prostatic tissue is rich in an acid phosphatase.¹³⁵ The Gutmans studied the acid phosphatase concentration in the prostate gland at different ages in the male and found that none was present in infancy but at the age of puberty the enzyme appeared in the gland. A significant contribution was added by the Gutmans when they reported that the serum acid phosphatase concentration was markedly elevated in patients with metastatic prostatic carcinoma.^{136,137} Shortly thereafter, Gomori¹³⁸ demonstrated the enzyme by histochemical technics in the prostatic epithelium of normal males and also its presence in high concentration in the epithelial cells of prostatic carcinoma.¹³⁸

In 1941 Huggins and his associates^{139,140} assembled the available evidence on the physiology of the prostate gland, integrated this with the recent advances in the knowledge of prostatic malignancy and proposed a hypothesis for rational therapy of cancer of this gland. The work of Kutscher and Wolbergs, the Gutmans and Gomori all pointed to the fact that a characteristic of normal, adult prostatic epithelium was the secretion of acid phosphatase. This, coupled with the observations that the enzyme was present in cancerous prostatic epithelium in the primary tumor and also in metastases¹⁴¹ together with the elevated serum acid phosphatase level, led to the conclusion that many carcinomas of the prostate are composed of adult epithelial cells. On the basis of previous observations that mature prostatic epithelium undergoes atrophy when normal androgen production is sharply decreased by castration or physiologically inactivated by estrogen administration, Huggins and his associates postulated that

significant clinical improvement should occur following bilateral orchiectomy in patients with far advanced prostatic carcinoma.^{139,140} Since this hypothesis could not be explored in experimental animals, it was tested by clinical trial.

In patients with far advanced prostatic carcinoma with metastases to bones Huggins and his co-workers followed changes in the serum acid and alkaline phosphatase concentrations as well as the clinical condition of the patient. The alkaline phosphatase proved to be a valuable objective measurement of alteration of the tumor because it provided an indication under these conditions of osteoblastic activity at the site of carcinoma metastases.¹⁴¹ It was demonstrated that following castration and/or administration of estrogens the serum acid phosphatase fell abruptly and there was clinical improvement. The alkaline phosphatase remained elevated for a longer time and returned to normal levels gradually. It was also possible to show that administration of androgen caused an elevation of the serum acid phosphatase concentration and clinical deterioration. These human experiments, therefore, appeared to confirm the thesis proposed and also offered promise of effective therapy for a common and devastating malignant disease.

Mechanism of Action. There are two subjects to be considered in this section: (1) the mechanisms involved in controlling the effects of androgen in the male by the administration of estrogen and (2) the effect of androgen deprivation on carcinomatous prostatic epithelium.

Normal function of the germinal epithelium and the interstitial cells (site of hormone elaboration) of the testis is dependent upon pituitary gonadotropins. Smith and Engle in a series of classical experiments¹⁴² demonstrated that ablation of the hypophysis in the male adult animal was followed by profound testicular damage. Characteristically, there were loss of gametogenic activity and changes in the accessory sex organs comparable to those seen in a

castrate animal. Moore and Price¹⁴³ produced a similar alteration in the morphology and function of the testes in normal animals by administration of estrogen. The deleterious effects of estrogen did not appear if a gonadotropic extract was injected simultaneously with the gonadal hormone. From evidence of this nature it has been concluded that estrogen does not have a harmful effect on the testes directly but inhibits the secretion of gonadotropic hormones by the pituitary gland, with the result that the gonads become atrophic.

In addition to the indirect mechanism Huggins presented evidence which would indicate that estrogen nullifies the action of testosterone by direct antagonism at the peripheral end organ.¹⁴⁴ It is to be noted that most of the evidence from animal experimentation is against the hypothesis that there is a direct antagonism between estrogen and androgen on specific cells. However, Huggins' observations in the castrate dog and studies in castrate men provide circumstantial evidence that in the case of prostatic epithelium estrogen acts peripherally and its effects are opposite to those of androgen.

Thus, the mechanism whereby estrogen impedes the growth of prostatic carcinoma or even causes it to regress is (1) through inhibition of pituitary function which in turn depresses the secretion of testosterone by the interstitial cells of the testis and (2) by direct antagonism of the action of testosterone on prostatic epithelium. Less clear is the mechanism of action of estrogens against prostatic carcinoma after castration. Theoretically, depression of adrenal androgen production could explain the salutary effects sometimes noted when estrogen therapy is administered to previously castrated patients. Assays of urinary hormone levels (gonadotropins and 17 ketosteroids) reported by Dean¹⁴⁵ suggested that estrogens decreased androgenic steroids by an indirect effect on the pituitary or by a direct action on the adrenal cortex. Clinically, however, this worker could not demonstrate that stilbestrol therapy was

effective after castration relapse in his patients. Other investigators have found that further beneficial effect may occur with estrogen therapy when a remission induced by orchiectomy is ended.

It now becomes necessary to inquire into the mechanism of action of testosterone on the prostatic epithelium in order to understand the fundamentals of androgen control therapy of prostatic carcinoma. Little is known about the immediate action of hormones on cellular physiology. In fact, the only precise information of this nature concerns the action of insulin in carbohydrate metabolism.¹⁴⁶ Although such detailed knowledge of the action of testosterone on prostatic epithelium is not available, Barron and Huggins have made observations of great interest and possible significance.¹⁴⁷ They studied, *in vitro*, the carbohydrate metabolism of prostatic epithelium obtained from dogs before and after castration or diethylstilbestrol administration. The oxidative phase of metabolism was characterized by determining the oxygen consumption in the presence of glucose and pyruvate. The anaerobic phase was studied by determining glucose fermentation under optimum conditions for glycolysis. Their experiments showed that when the prostate was deprived of androgen support there was a marked decrease in the oxidative phase of carbohydrate metabolism as indicated by a diminished Q_{oxygen} and Q_{pyruvate} . No change was noted in the anaerobic phase of carbohydrate metabolism. Although these observations do not specifically explain the action of testosterone, they indicate the fundamental role played by this hormone in the cellular physiology of prostatic epithelium.

Clinical Application. Since the first reports by Huggins^{139,140} on the effect of orchiectomy and of Herbst¹⁴⁸ on use of estrogens in the therapy of prostatic carcinoma, there have been many publications which have confirmed the beneficial action of androgen control on the disease.¹⁴⁹⁻¹⁶⁰ From these articles and many others it is possible to make some general statements

about the immediate results to be anticipated in those patients responding satisfactorily. From the patient's viewpoint the most dramatic effect is relief of pain. Associated with this there is a sense of well being, an increased appetite and a gain in weight. Frequently the anemia associated with far advanced disease will respond to iron therapy. Objectively, the serum acid phosphatase usually drops to normal levels; the alkaline phosphatase may first rise, then gradually fall; soft tissue metastases regress and in some instances there is evidence of healing of bone metastases. In most patients there is evidence by rectal palpation of decrease in size of the primary tumor with attendant relief of obstructive urinary signs and symptoms. Neurologic symptoms due to pressure or traction on nerve roots, particularly the cauda equina, are also relieved. Serial biopsy studies by Ferguson¹⁵³ and by Schenken et al.¹⁶¹ revealed alterations in the nuclei of the epithelial cells, consisting of reduction in size, progressive condensation of the chromatin, loss of nucleoli, loss of mitotic figures and pyknosis. The cytoplasmic changes consisted of progressive vacuolization and finally rupture of the cell membrane. After some months most of the malignant tissue was replaced by scar tissue. Significantly, however, it was noted that there never was complete disappearance of malignant cells. Dean mentions¹⁴⁵ one patient with histologically proven prostatic carcinoma who died a cardiac death four years after institution of androgen control therapy. Despite careful autopsy study no microscopic evidence of residual cancer was disclosed in this man. This observation may indicate that an occasional cure will result from androgen control therapy.

As has been indicated not every case of prostatic carcinoma responds satisfactorily to androgen control therapy. Huggins has suggested that the explanation for this is related to the cellular characteristics of the malignancy. The anaplastic epithelial tumor does not, in his opinion, react to androgen withdrawal as does adenocarcinoma. This

would be in keeping with the thesis that adenocarcinoma is made up of mature epithelial cells and therefore responds in a manner analogous to normal epithelium whereas the undifferentiated type of carcinoma is not subject to hormonal influences. This explanation has both adherents and antagonists, i.e., those who have found that the cell type is not a determining feature in the response to therapy.

There are many other questions of a practical nature which will require additional experience to answer definitely. At present, for example, it is impossible to state unequivocally that castration is superior to estrogen therapy or the reverse, or that a combination of orchiectomy and estrogen is the best therapeutic regimen. Most urologists utilize both means for decreasing androgen, but there is considerable disagreement on the order in which the two procedures should be carried out. It is generally agreed that castration results in a more rapid remission of signs and symptoms but there is a surgical risk involved, particularly in the debilitated patient, and the psychologic barrier to castration is important in some instances. Following castration, there may be symptoms of vasomotor instability in the form of hot flushes and sweating, but these can be controlled easily by estrogens. Administration of estradiol or synthetic estrogens also results in toxic manifestations in some instances. One of these is gastrointestinal upsets, particularly with use of stilbestrol. Most troublesome is enlargement and tenderness of the breast due to the action of estrogen on the ductal epithelium.^{162,163}

Following introduction of androgen control therapy for prostatic cancer, there was a wave of intense enthusiasm as a result of the dramatic immediate responses and hopes ran high that a cure for this type of malignancy had been found. A sufficient time interval has now passed to assess the results of therapy and a very much more restrained attitude must be taken. In Table II the results of therapy of several series of patients who have been observed

for two years or more are summarized. The statistics of the control series are valid for comparison with the specific therapy series because the patients were treated surgically for relief of urinary obstruction and also were treated with sulfonamides for urinary tract infections when indicated. These are important supportive measures in prolonging life in prostatic malignancy as can be demonstrated easily by comparing the mortality figures for this control series of patients with those obtained by others before the general employment of transurethral surgery and bacterial chemotherapy.¹⁶⁸ It is evident from the data in Table II that androgen control therapy of prostatic cancer has significantly prolonged life. For example, in the control series 62 per cent of the patients died one year after there was evidence of dissemination of the malignancy from the primary site, whereas the statistics of the several treated series indicate that only about 40 per cent of the patients were dead after one year. However, it is also to be noted that as the period of observation lengthens, the mortality figures in the treated series more closely approach the control values.

The explanation for development of refractoriness to androgen control therapy in prostatic malignancy is not yet known although it has been suggested that one of the causes may be a change of the malignant cell from a mature prostatic epithelial cell to a less well differentiated, more anaplastic type. Of interest in this regard is the observation¹⁶⁹ that adenocarcinoma cells of the human prostate, cultivated in the anterior chamber of guinea pig eyes, lose their power to produce acid phosphatase, yet after serial transplantation through several rodent hosts they maintain their typical microscopic appearance and malignant characteristics. These findings would point to the fact that de-differentiation of cell type can and does take place in this neoplasm.

Comment. To date androgen control therapy of prostatic cancer has provided the single, most outstanding, practical con-

tribution to the chemotherapy of malignancy. It can be stated unequivocally that castration and/or estrogen administration should constitute a part of the routine therapeutic management of all cases of disseminated carcinoma of the prostate gland.

SEX HORMONES IN THE THERAPY OF CARCINOMA OF THE BREAST

Background and Rationale. The existence of a relationship of the ovarian hormones to cancer of the breast was first clearly demonstrated by Leo Loeb and his associates. They found that the incidence of spontane-

TABLE II
ANDROGEN CONTROL THERAPY OF PROSTATIC MALIGNANCY

Authors	Control (Vest and Frazier)		Vest and Frazier		Huggins		Alyea		Emmett and Greene		Nesbit and Plumb		Herger and Sauer	
No. of Patients	74		74		20		37		133		75		109	
Months after Onset of Rx	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive	Per Cent Dead	Per Cent Alive
0-6	20	80	5	95	5	95	13	87	8	92	16	84
6-12	38	62	14	86	20	80	16	84	24	76	19	81	28	72
12-18	57	43	19	81	33	67	42	58	29	71	40	60
18-24	62	38	28	72	55	45	35	65	45	55	37	63	49	51
24-30	66	34	37	63	43	57	60	40
30-36	69	31	42	58	54	46	67	33
36-42	69	31	43	57	61	39	73	27
42-48	73	27	65	35	67	33	74	26
48-54	76	24	74	26
54-60	77	23	75	25
60-72	80	20
72-84	82	18

Vest and Frazier, *J. Urol.*, 56: 97, 1945.

Huggins, *J. A. M. A.*, 127: 63, 1945.

Alyea, *J. Urol.*, 53: 143, 1945.

Emmett and Greene, *J. A. M. A.*, 127: 63, 1945.

Nesbit and Plumb, *Surgery*, 20: 263, 1946.

Herger and Sauer, *New York State J. Med.*, 47: 494, 1947.

In addition to the tremendously significant advance in practical therapeutics this type of treatment has greatly stimulated laboratory investigation of cancer chemotherapy. The results have demonstrated the effectiveness of alteration of the internal environment in retarding the neoplastic growth of prostatic epithelium. It is possible that other changes in the internal environment which are compatible with function of the normal cells of the host may be incompatible with the existence or growth of other types of neoplastic cells.

ous carcinoma of the breast in mice was significantly decreased by castration.^{170,171} The importance of the stimulative action of estrogen on the development of carcinoma of the breast was brilliantly demonstrated experimentally by Lacassagne.¹⁷² Using a strain of mice in which 72 per cent of the females characteristically succumb to adenocarcinoma of the breast but in which no males develop spontaneous breast tumors, he administered estrone to the latter over prolonged periods. Initially, a network of ducts developed in the axillary and inguinal

regions of the treated males. This was followed by proliferation of the ductal epithelium and, between the fourth and tenth months, a rapidly growing adenocarcinoma evolved from which the animals died, either with ulceration of the tumor through the skin or with pulmonary metastases. Even more impressive were Lacassagne's experimental results in which estrogen carcinogenesis was demonstrated in a strain of mice in which the incidence of spontaneous carcinoma of the breast was very low. In these experiments after twelve to eighteen months of estrogen administration all of the mice died with malignant tumors of the breast. As a result of these observations Lacassagne suggested the possibility that antagonism of estrogen by androgen might provide a significant therapeutic advance in the treatment of human mammary cancer.

This suggestion was tested experimentally in mice¹⁷³⁻¹⁷⁵ and it was found that the male sex hormone, testosterone, indeed could prevent the appearance of breast cancer in strains in which spontaneous mammary carcinoma incidence was high. However, it is to be noted that the experiments were conducted by administering the androgen very shortly after the birth of the animals and continuing it over long periods. Under these conditions the ovary never became functional and the breasts of the female mice remained rudimentary. Loeser¹⁷⁶ delayed androgen therapy until later in the life of the mice and found that if the treatment was instituted only shortly before the expected appearance of the malignancy no protection was afforded.

Although the experimental evidence of an inhibitory effect of androgen on either the development or growth of carcinoma of the breast was not convincing, there were scattered clinical trials of this form of therapy in inoperable breast cancer in humans. Ulrich,¹⁷⁷ Loeser¹⁷⁶ and Fels¹⁷⁸ reported encouraging results in a few patients. Marked impetus to use of androgen therapy in far advanced carcinoma of the breast has been provided by a series of

reports by Adair and Herrmann in the past two years. These will be discussed in detail in the section on clinical application.

Mechanism of Action. In order to understand the mechanisms by which androgenic hormone could conceivably retard the progress of cancer of the breast it is necessary to review briefly the endocrine factors which influence the histology and physiology of the mammary gland.

Ovarian Hormones: The importance of estrogenic follicular hormone in the development and function of the breast has been clearly established by many observations, both experimental and clinical.^{179,180} It now is generally accepted that in the human, proliferation of the duct systems and growth of the connective tissue framework of the breast is dependent upon the estrogenic hormone. Progesterone, the hormone of the corpus luteum, is necessary for the development of the alveoli and lobules of the breast. Under the influence of progesterone, after the breast has first been prepared by estrogen, the epithelium is converted to the typical secretory type. It is important to note, however, that although histologically the gland looks like a secretory organ following estrogen plus progesterone administration, lactation cannot be induced by these hormones alone.¹⁸¹

Hormones of the Pituitary Gland: A specific lactogenic hormone, prolactin, has been isolated from the anterior hypophysis. This induces lactation in the experimental animal after the breast has been suitably stimulated by estrogen and progesterone.¹⁸² Thus, it is apparent that a delicate and rather intricate balancing of the hormones of the pituitary and ovaries is essential for normal function of the mammary gland.

It has been reported that there is another hormone from the anterior pituitary, mam-mogen, which is essential for the development and growth of the breast.¹⁸³ However, the experimental evidence for this additional component of the anterior pituitary hormone is not convincing and more recent work with highly purified prolactin indi-

cates that this fraction alone can reproduce all of the experimental observations attributed to mammogen.¹⁸⁴

Hormones of the Adrenal Cortex: In addition to the corticosteroids which have very significant physiologic functions in modifying electrolyte, protein and carbohydrate metabolism, estrogenic and androgenic hormones have been isolated from the adrenal glands.¹⁸⁵ The extent to which the adrenal cortical sex steroids influence the reproductive system under normal conditions is not known. However, it is important to appreciate that after castration the sex hormones continue to be excreted in the urine in appreciable amounts, indicating that the adrenal cortex is able to secrete significant quantities of these hormones.

With this background of information on the hormones which influence the breast and their sites of elaboration, the mechanisms whereby androgenic hormone could antagonize the physiologic actions of other hormones may be considered. As has been discussed in the section on use of estrogens in prostatic malignancy there is a reciprocal relationship between the gonadotropins of the pituitary and the hormones of the gonads. Thus, theoretically, it would be anticipated that suitable doses of androgenic hormone would depress pituitary activity and secondarily inhibit the physiologic function of the gonads. It had been shown that administration of testosterone to women decreases the urinary excretion of pituitary gonadotropins and coincidentally there is evidence of suppression of ovarian function.¹⁸⁶ Not only is the elaboration of gonadotrophic hormones of the pituitary diminished by excessive gonadal hormone administration, but also all of the other secretions of the hypophysis are depressed. If adrenotrophic hormone from the pituitary is decreased, the release of sex steroids by the adrenal cortex is concomitantly lowered as Long and his collaborators have shown.¹⁸⁷

There also are both experimental and clinical observations which suggest that androgen may peripherally antagonize the effects of estrogen. Thus, Shorr and his

associates¹⁸⁸ have shown that the cornifying action of estrogen on the vaginal epithelium of postmenopausal women can be reversed by simultaneous administration of testosterone. The experiments of Robson¹⁸⁹ on ovariectomized mice, in which vaginal cornification by estrogen was prevented by concomitant administration of androgen, also indicate a peripheral neutralizing action of testosterone. It is to be noted, however, that the evidence for a direct peripheral antagonism of the sex hormones is subject to question inasmuch as the contribution of the adrenal sex steroids has not been controlled in these experiments. There is circumstantial evidence indicating that a minute amount of progesterone is necessary for the complete response of estrogen in an appropriate end organ. It has been shown that progesterone is elaborated by the adrenal cortex, and it is presumed that it is this source of progesterone which makes possible the evident complete replacement of the follicular hormone by synthetic estrogens after ovariectomy. In experimental animals such as the hamster, in which no progesterone is elaborated by the adrenal cortex, it is impossible to duplicate the characteristics of estrus by estrogen administration after castration. Thus, the experiments which purport to demonstrate a peripheral antagonism of estrogen and androgen may, in fact, conceivably be another manifestation of pituitary inhibition in which the adrenotrophic hormone is suppressed.

In addition to the antagonism of estrogen by androgen it is necessary to consider another physiologic action of testosterone which may be significant in understanding the results of therapy with this hormone in breast malignancy. Albright,^{190,191} Kenyon,¹⁹² Abels et al.¹⁹³ and others have shown that testosterone affects protein metabolism in man. From their observations that administration of the hormone is followed by a positive nitrogen balance without elevation of the serum non-protein nitrogen they concluded that protein anabolism is stimulated or protein catabolism is in-

hibited. It has also been shown that testosterone induces a positive calcium balance. Albright presents an attractive hypothesis in which the mechanism of this observation is ascribed to increased osteoblastic activity with deposition of calcium in bone.¹⁹⁰

Clinical Application. *Androgen:* Metastases from carcinoma of the breast may be limited to the soft tissue or to the skeletal system or they may involve both soft tissue and bone. As will be seen in the following comments the localization of metastatic carcinoma of the breast appears to be a significant factor in the response to chemotherapy.

In 1942 Farrow and Woodard¹⁹⁴ reported a carefully observed series of thirty-three patients with bony metastases who received testosterone propionate in doses of 5 to 25 mg. on six to twelve occasions. Their results were, on the whole, discouraging and in fact they presented evidence which indicated that in some instances the progress of the neoplasm was accelerated. However, in 1946 Herrmann and Adair¹⁹⁵ published results of androgen therapy of metastatic breast carcinoma which were more encouraging. To date Adair and his associates have reported twenty-seven cases of patients with advanced carcinoma of the breast treated with testosterone propionate, giving data in sufficient detail for tabulation of results.¹⁹⁵⁻¹⁹⁷ In later communications Adair stated that 450 patients had been so treated but gave no details.^{198,199} Preliminary reports by Schwander and Marvin,²⁰⁰ Jones²⁰¹ and Davison and Letton²⁰² substantially confirm the observations of the Memorial Hospital group.

At the present time the recommended dosage of testosterone propionate is 100 mg. by intramuscular injection three times weekly for a period of eight to ten weeks. This total dosage of 2,400 to 3,000 mg. is far in excess of that employed by Farrow and Woodard and may be significant in explaining the difference in clinical response noted by the two groups.

Table III presents a brief summary of the results of androgen therapy in the twenty-seven cases reported by Adair and his

associates. The pertinent facts were abstracted from the published case histories. As can be seen testosterone is rarely efficacious in the control of soft tissue metastases of carcinoma of the breast and the course of the lesion is not altered. However, of the fifteen patients with osseous involvement by the malignancy, only two patients failed to receive any benefit. In the remaining thirteen individuals the pain produced by the bone metastases was relieved and there was a feeling of well being. Occasionally, there was roentgen evidence of bone healing, however, this was only temporary. Whether or not life has been significantly prolonged in the patients with osseous metastases is difficult to state. Reference to the table shows that in ten of these fifteen patients there was either marked dissemination of the disease in the osseous system or the appearance of soft tissue metastases. In the latter group it would be anticipated that death would occur within one year.

Associated with the relief of bone pain following testosterone therapy, there are changes in the blood chemistry which are of importance in evaluating the success of therapy in the presence of osseous metastases. The serum calcium is usually elevated above the normal concentration. Following administration of androgen, the calcium level drops toward normal. This is interpreted as evidence of deposition of calcium in new bone. In two of the reported cases the calcium concentration rose following testosterone, with mild symptoms of calcium intoxication; x-ray examination of the metastatic lesions in the bones revealed progression in both instances. It therefore may be concluded that a significant elevation of the calcium level during testosterone treatment is an indication to discontinue therapy as it is probable that the malignant cells are being stimulated rather than depressed. In the majority of successfully treated patients the serum alkaline phosphatase rose as the calcium fell, indicating increased osteoblastic activity. In these patients there was also a gain in weight up to almost 10 Kg. which was promptly lost

when the therapy was discontinued. This probably is largely due to the effect of testosterone on nitrogen retention rather than an expression of increased caloric intake since it did not persist even though

Estrogen: Estrogenic therapy of carcinoma of the breast has also been reported. The proposed rationale is highly speculative, and is perhaps most significant as an expression of the great need for better understand-

TABLE III
RESULTS OF ANDROGEN THERAPY IN TWENTY-SEVEN PATIENTS WITH METASTATIC CARCINOMA OF THE BREAST

Case No.*	Age	Evident Distribution of Disease	Duration of Remission (months)	Remarks
1A	63	Soft tissue	5	Died of disease nine months after institution of therapy
Not given		Soft tissue	0	Died with pulmonary metastases without response
Not given		Soft tissue	0	Died with liver metastases without response
Not given		Soft tissue	0	Died of disease; no response to therapy
Not given		Soft tissue	0	Died of disease; no response to therapy
Not given		Soft tissue	0	Died of disease; no response to therapy
1B	39	Soft tissue	0	Living one year after onset of therapy; disease constantly progressive
2B	56	Soft tissue	0	Terminal six months after institution of therapy
3B	54	Soft tissue	0	Living fifteen months after onset of androgen therapy; lesion controlled by x-ray
4B	52	Soft tissue	0	Living two months after institution of androgen therapy; lesion progressive
5B	40	Soft tissue	0	Living three months after institution of androgen therapy; no improvement
6B	27	Soft tissue	3.5	No further follow-up report
2A	47	Osseous	5	Evidence of cerebral metastases plus pulmonary metastases developed; terminal eight months after institution of androgen therapy; no recurrence of bone metastases
3A	42	Osseous and soft tissue	9	Terminal thirteen months after institution of androgen therapy with widespread osteolytic lesions of bone
4A	44	Osseous	18	Asymptomatic at last report; has received repeated courses of androgen therapy
Not given		Osseous	0	Calcium intoxication and rapid progression of osteolytic lesions
1C	60	Osseous	8	Asymptomatic at last report
2C	59	Osseous	6	Asymptomatic at last report
3C	59	Osseous	6	Asymptomatic at last report
4C	43	Osseous	3	Asymptomatic at last report
5C	58	Osseous	6	Asymptomatic at last report but evidence of progression of metastatic lesions
6C	40	Osseous	7	Asymptomatic at last report; progression of osteoblastic metastases
7C	45	Osseous	4	Pulmonary metastases appeared at this time; no follow-up
8C	55	Osseous and soft tissue	1	Progression of pulmonary metastases
9C	39	Osseous	1	Terminal four months after institution of androgen therapy, with evidence of progression of bone metastases
10C	62	Osseous	0	Died two months after institution of therapy
11C	53	Osseous	5	Evidence of liver metastases at this time

* The letters after the case numbers refer to the source of the information. A, ¹⁹⁵; B¹⁹⁶; C, ¹⁹⁷.

the patient remained asymptomatic and the caloric intake remained constant.

The side effects of testosterone consisted of hirsutism, acne vulgaris, deepening of the voice, suppression of menstruation and increased libido with enlargement of the clitoris. None of these masculinizing effects necessitated discontinuance of the drug.

ing of the biology of this disease. From the fact that the incidence of malignant tumors of the breast is high between the ages of forty and sixty years and the fact that this is also the age range in which the incidence of menopause is highest the following hypothesis has been set forth:²⁰³ With the onset of the climacterium, there is either atrophy

or dysfunction of the ovaries with an over-secretion of hormones of the anterior pituitary (follicle-stimulating hormone, luteinizing hormone and prolactin) and concomitantly there is an alteration in the cellular activity of breast tissue. An imbalance develops between the various endocrine glands resulting in thyroid hypo- or hyperactivity and possibly in hyperactivity of the suprarenal cortex. The cellular activity of the breast, no longer under the control of ovarian hormones and possibly stimulated by other hormones, becomes abnormal and in certain instances frank malignancy develops. Thus, the replacement of estrogenic hormone by restoring the normal hormone balance might provide an environment in which the malignant cells are unable to survive.

An alternate rationale for the use of estrogens in carcinoma of the breast has been suggested by the observation of Haddow that carcinogenic hydrocarbons under certain conditions possess the property of retarding the growth of normal and malignant tissue in experimental animals.²⁰⁴ On the assumption that estrogens are significant in the etiology of human carcinoma of the breast they theoretically might also retard the growth of the tumor.

These hypotheses have been put to clinical test in a number of patients and the result in more than 300 cases have been reported in the literature. In a symposium on the subject²⁰⁵ ten British observers pooled their experience with 168 patients. Of these, one hundred were less than and sixty-eight were over sixty years of age. Although detailed reports are not available, it may be inferred from the discussion that under the age of sixty, estrogen therapy accelerated the progress of malignancy and was therefore definitely contraindicated; in patients over sixty there was regression of the soft tissue metastases and of the primary tumor in approximately 50 per cent of the cases. There is no follow-up report on these patients so that it is impossible to make any statement about the effect of estrogen therapy on prolongation of life. Haddow

and his associates,²⁰⁶ Nathanson²⁰⁷ and Herrmann et al.²⁰⁸ also have treated patients with synthetic and natural estrogens with similar results.

Comment. From the evidence presented it may be concluded that large doses of androgenic hormone will provide relief of pain and a subjective sense of well being in patients with carcinoma of the breast metastatic to bone. Although objective x-ray evidence of bone healing is rarely seen, there frequently are changes in the blood chemistry which would indicate that reparative processes in the bone are occurring. In any event it is apparent that the therapy provides only temporary palliation.

The possible mechanisms for the observed effects of androgens in carcinoma of the breast have been discussed. In view of the marked difference in the clinical response to androgen therapy depending upon the localization of the metastases it is questionable whether antagonism of estrogen by testosterone plays any significant part in the results. It is difficult to believe that antagonism of estrogen would be effective in retarding neoplastic growth in the bone but be ineffective when the same neoplasm was growing in soft tissues. A more acceptable explanation for the observed effects of testosterone therapy of breast cancer may be derived from the known changes in protein and calcium metabolism produced by this hormone. The fact that responses are limited to those patients with osseous metastases is then more understandable.

Radiotherapy has been employed effectively in the palliation of metastatic breast carcinoma to the bones and with less regular success in the soft tissue metastases for a long period of time.¹ Since this is so, it may justifiably be asked why androgen therapy should be considered. There are at least three situations in which this form of chemotherapy of inoperable carcinoma of the breast with osseous metastases is indicated: (1) when radiotherapy is not available, (2) when the dissemination of symptomatic metastatic lesions in the

skeletal system is so great that radiotherapy is not practical and (3) when it is no longer permissible to employ radiotherapy because the pain has not responded to x-ray treatment, the tumor has become refractory to x-ray or the skin overlying the involved area cannot withstand further radiation.

Estrogen therapy of carcinoma of the breast should be reserved for patients who are well past the menopause and who have radioresistant soft tissue metastases. Under these conditions estrogens may be employed as a last resort. It is necessary to observe the patient closely during therapy so that the drug can be discontinued with the first evidence that the neoplasm is being stimulated rather than depressed.

NITROGEN MUSTARD

Background and Rationale. The emergence of nitrogen mustard as a significant chemotherapeutic agent against malignancy is a fascinating and dramatic story. The development of nitrogen mustard is inextricably linked to the World War I vesicant agent, "mustard gas." Dichloroethyl sulfide, popularly known as yellow cross gas, Lost and Yperite as well as mustard gas, was first prepared by Richie in 1854, independently synthesized by Guthrie and Niemann in 1860 and fully described both chemically and physiologically by Victor Meyer in 1886.²⁰⁹ These chemists appreciated the highly toxic actions of the compound and Meyer noted that even more striking than its vesicant properties was its lethal action in small doses when administered parenterally.

During the spring of 1917 the Germans carried out secret field tests with such satisfactory results that they adopted dichloroethyl sulfide as an artillery-shell filling and accumulated a large quantity of these (yellow cross) shells before the Allies were aware of this development. On the night of July 12, 1917, the Germans loosed an artillery bombardment against the British front near Ypres in Flanders. An indication of the devastating effect produced by this agent is given in the statistics of the first

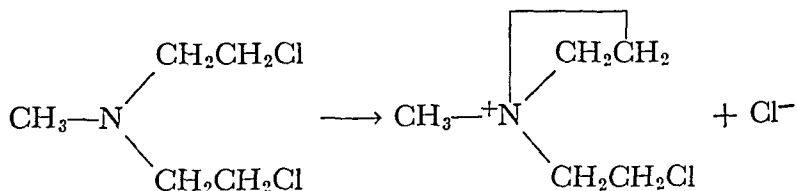
three weeks of mustard gas use. Fourteen thousand, two hundred seventy six cases of gas-shell poisoning were admitted to the British casualty stations and about 500 deaths occurred among these patients.²¹⁰

Descriptions of mustard gas intoxication soon appeared in the medical literature. At first attention was focused on the local actions as manifested by skin vesication which frequently progressed to deep ulcers, conjunctivitis, photophobia and lacrimation, irritative laryngitis, bronchitis with intractable cough, aphonia and often secondary bronchopneumonia.^{211,212} Somewhat later, however, it was appreciated that serious systemic toxicity was not uncommon, and the Krumbhaars called attention to the characteristic finding of leukopenia in the fatal cases due to marked depression of the bone marrow function.²¹³ Laboratory studies were carried out in order to define the mechanism of action of dichloroethyl sulfide, and by the termination of the war the hypothesis of Lynch, Smith and Marshall²¹⁴ was largely accepted. These workers believed that the lipid solubility of the compound facilitated its localization in the cell. At this site hydrolysis took place with the liberation of hydrochloric acid thereby producing a cytotoxic effect.

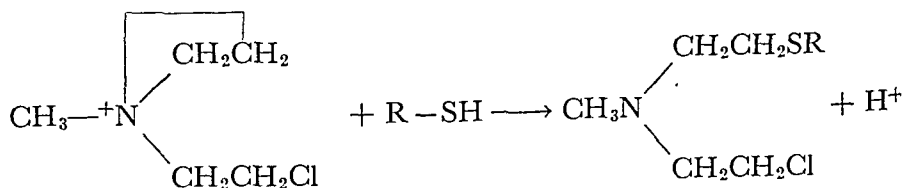
In the interim between World Wars I and II there was continued activity in the chemical warfare laboratories of the French and Germans. By the time the United States entered the war it was known that the enemy had available, in addition to dichloroethyl sulfide and other potential chemical warfare agents, the nitrogen analogs of mustard gas, the so-called nitrogen mustards. The Allies strongly believed that advances in the treatment of gas casualties could be made only when the mechanism of action of the toxic agents was better understood. To this end chemical, physiologic and pharmacologic studies were initiated in university and government laboratories. Observations on the biologic actions of nitrogen mustards were greatly facilitated by the fact that crystalline hydrochloride salts of these compounds could be

prepared. Gilman and Philips have summarized the pharmacology of the nitrogen mustards.²¹⁵ Clinical applications of these compounds in the therapy of malignant lymphomas was suggested by the susceptibility of lymphoid tissue to the cytotoxic action of the nitrogen mustards in sublethal doses.

Mechanism of Action. A clear understanding of the pharmacologic actions of nitrogen mustards depended upon clarification of the chemistry of the compounds.²¹⁶⁻²³⁰ Stein, Fruton, Stahmann, Bergmann and Golumbic demonstrated in a series of experiments that the stable, crystalline nitrogen mustards and sulfur mustard undergo transformation to a cyclic onium cation when they are put into solution at the pH of body fluids, with the liberation of Cl^- which is highly reactive chemically. This ring formation, using methyl bis (β -chloroethyl) amine (the nitrogen mustard most widely used therapeutically) as the example, may be thus illustrated:



It was quickly appreciated that the biologic activity of the nitrogen mustards was dependent upon the ring form which reacted avidly with a great variety of functional groups of compounds with physiologic significance. For example, the reaction of the ethylene immonium cation with compounds having sulfhydryl groups may be diagrammed:



Many pharmacologic actions of the nitrogen mustards have been described, these depending upon the dose administered.^{215, 231-242} Comments, however, will be

limited to the biologic effects produced with doses comparable to those in human therapy. Under these conditions the outstanding actions of the drug are reflected in the response of hemopoietic tissue and the gastrointestinal tract.²³⁷⁻²³⁹ After intravenous administration to a normal dog there is a latent period of one-half to one hour during which the animal appears entirely unaffected. The dog then begins to salivate and this is quickly followed by vomiting. The vomiting may continue intermittently for a period of several hours. The mechanism of the emesis is presumed to be a reflex initiated in the gastrointestinal tract because as the dose of nitrogen mustard is increased the gastrointestinal symptoms become more severe with protracted vomiting, diarrhea and histologic evidence of hemorrhagic necrosis of the gut epithelium. Within twenty-four hours after the injection of nitrogen mustard the leukocytes of the peripheral blood begin to decrease and a differential examination reveals a relative

lymphocytopenia. In the next few days there is further depression of the white blood count and granulocytopenia develops. The bone marrow at this time is hypoplastic with a decrease of all elements and the lymphoid tissue of the body shows widespread destruction. With these doses, thrombocytopenia is inconstantly present and anemia is not observed for several

weeks, if at all, probably due to the longer life span of erythrocytes as compared with other cells. At this dosage level the depression of hemopoiesis is reversible and within

three weeks the bone marrow and peripheral blood picture are normal.

The site of cellular action of the nitrogen mustards has been localized in the nucleus. In a fascinating series of experiments Bodenstein and Gillette have observed the morphologic changes in embryonic cells exposed to low concentrations of the drug.^{243,244} Directing their attention especially to the exposed ectoderm of *Amblystoma punctatum* they noted that all mitotic activity had come to a standstill forty-eight hours after exposure to nitrogen mustard. The cells were arrested in the interphase state of their mitotic cycle. However, the nuclei of these cells continued to grow, attained a giant size and ultimately broke down into a number of roundish fragments. Friedenwald and his colleagues studied the cellular changes induced by nitrogen and sulfur mustard in adult tissue.^{245,246} Their test object was the corneal epithelium of the rat. Exposing the eye to very dilute solutions of the mustards, they also observed nuclear fragmentation and death of the cell. They concluded that this phenomenon was a form of pathologic mitosis. Friedenwald reported that death of the corneal epithelium, characterized by karyolysis and by pyknosis, was produced by progressively increasing the dose of mustards.

That the mustards can affect the most intimate physiologic mechanisms of the cell nucleus is shown by the experiments of Auerbach, Robson and Carr. These investigators exposed the fruitfly, *Drosophila melanogaster*, to low concentrations of sulfur mustard and observed striking chromosomal alterations as manifested by increased incidence of sex-linked lethal genes and chromosomal transformations.^{247,248} Stahmann and Stauffer²⁴⁹ induced mutants in *Penicillium notatum* by exposing the spores to nitrogen mustards, and Horowitz and his associates produced mutations chemically in *Neurospora crassa*.²⁵⁰ In all of these investigations the effects of the mustards on chromosomes were compared with those produced by radiant energy and

these were found very similar quantitatively and qualitatively.

It has been repeatedly noted by the investigators who have studied the biologic actions of the mustards that these chemicals mimic the effects of x-ray and ultraviolet radiation to a remarkable degree.^{246,251,252} It is possible that a clear understanding of the mechanism of action of the mustards will also provide some insight into the mechanisms whereby radiant energy produces its effects on cells.

Clinical Application. Following the pharmacologic observations on the cytotoxic effects of the nitrogen mustards (bis and tris (β -chloroethyl) amines) on a variety of histologic cell types, Goodman, Gilman and their associates and Jacobson and his colleagues initiated therapeutic trials with these drugs in humans.^{253,259} Striking results in neoplasia of the lymphatic and hemopoietic systems prompted a more extensive study under the direction of the committee on Growth of the National Research Council. It would be premature to draw final conclusions regarding the chemotherapeutic efficacy of the nitrogen mustard compounds used clinically thus far or to assume that related compounds with a higher selectivity of action for neoplastic tissue will not be forthcoming. Attention should be called to the fact that no cures have been reported in any of the numerous types of disease processes in which these drugs have been used and it should be stressed that therapy with nitrogen mustards (abbreviated HN) therefore remains only palliative in nature.

Administration. Because of the high incidence of phlebothrombosis at the injection site and the quantitatively greater leukopenia following its use, as well as the failure to demonstrate superior clinical results to those seen with the methyl bis (β -chloroethyl) amine (HN_2), the tris (β -chloroethyl) amine (HN_3) has been largely discarded as a therapeutic agent in favor of HN_2 . Most clinical reports deal with results obtained with this latter drug although observations on new compounds are being made.²⁵⁴ HN_2 is dispensed in sterile bot-

tles containing 10 mg. of the drug as the hydrochloride. In clinical practice the crystalline material is dissolved by the addition of 10 cc. of sterile 0.9 per cent saline to the bottle, the calculated dose is withdrawn in a sterile syringe and injected within five minutes after mixing into the rubber tubing of a rapidly running intravenous infusion. The commonly employed dosage schedule is 0.1 mg. of HN_2 per Kg. of body weight daily for four days, giving a total of 0.4 mg. per Kg. of body weight per course of therapy. Variations of this schedule can be utilized, such as 0.2 mg. per Kg. of body weight on two successive days; or one can use either of these dosage schedules with rest days between successive doses in the case of debilitated or frail patients. Neoplasms rarely are susceptible to doses as small as 0.04 mg. per Kg. of body weight.²⁵⁵ Because of the narrow margin between the therapeutic and toxic ranges, doses in excess of those mentioned are hazardous.²⁵⁶ Hypnotic doses of barbiturate compounds administered an hour before and immediately after each treatment frequently diminish nausea and vomiting following drug injection. Other measures such as pyridoxine and antispasmodics have not significantly alleviated these toxic side reactions. Subsequent courses of therapy should be undertaken only after careful evaluation of the response of the bone marrow and neoplastic process to the initial course of treatment. Spurr has stated that six weeks should elapse between courses²⁶⁰ while others²⁵⁸ wait only two weeks in some cases before resuming mustard therapy.

The decision as to whether patients should be hospitalized for treatment depends largely on their general state of health, the extent of the neoplastic or other disease process to be treated, and the clinical facilities available. Suffice it to say that therapy should be assiduously supervised and post-treatment observation for signs of drug toxicity should be insured. In most clinics careful check on the peripheral blood picture is made frequently, beginning several days after the completion of a course of therapy

until marrow regeneration is nearing completion (usually two, occasionally three weeks later). Follow-up studies, such as marrow or tumor biopsies, x-rays, photographs, etc., are of the greatest clinical importance in evaluating the therapeutic response and should be resorted to as frequently as possible.

Toxicity. Early workers conclusively showed that the nitrogen mustards were not tumor-selective in their action but damaged other cell types as well. To date no compound has been found with highly specific affinity for neoplastic tissue alone. Due to the lack of selectivity of action with currently used drugs damage to other tissues is reflected in the form of several types of toxic reactions which may be conveniently grouped into immediate and late effects:

Immediate Toxic Effects: (1) Pain at the injection site has been most frequently seen when active nitrogen mustard has come into contact with subcutaneous tissues due to faulty venipuncture technic. Areas so contaminated may undergo necrosis and ulceration but usually progress only to moderate inflammation and subsequent healing with induration and pigmentation.²⁵⁸ (2) Phlebothrombosis at injection sites was observed more frequently in earlier clinical trials with HN_3 . Present use of HN_2 administered into the rubber tubing of a rapidly flowing intravenous infusion has reduced this complication to a rarity. (3) Nausea and vomiting are seen in a high percentage of patients within one to eight hours after treatment, persisting as long as forty-eight hours thereafter in some patients. The severity and duration of individual susceptibility, age of the patient (less frequent in children) and adequacy of sedation rather than the size of the dose administered. Administering the drug several hours after the last meal of the day to a patient who is under proper sedation, appears to be of real benefit in decreasing or obviating the emetic effects of these compounds.²⁵⁵ Accompanying these gastro-

intestinal disturbances, transient anorexia, weakness, headache and weight loss of several pounds are the rule for the next twenty-four to forty-eight hours.

Delayed Toxic Effects: Available data indicate that delayed toxic effects are limited to the hemopoietic system at therapeutic dosage levels and constitute the most potentially dangerous toxic manifestations of nitrogen mustard therapy. Cytotoxic action on bone marrow and lymphatic tissue may progress to complete aplasia of the former and widespread fragmentation of the latter. Careful clinical studies of these phenomena by several groups²⁵⁸⁻²⁶⁰ will be briefly summarized.

Peripheral Blood—The initial change noted is a lymphocytopenia appearing within twenty-four hours after initiation of therapy and progressively increasing over the ensuing six to eight days, with a return to normal levels within two weeks. Monocyte levels parallel the changes seen in the lymphocyte series. During the maximum depression period degenerating cells of these two series have been seen in Hodgkin's disease patients and attention is called to their resemblance to blast forms in stained smears.²⁶⁰ Along with these changes the total leukocyte count declines progressively for fifteen to twenty-one days to variable levels, this fall being largely due to neutropenia. Degenerative morphologic changes in the granulocytes and the appearance of myelocytes in the blood smear may be seen during development of this leukopenia. Recovery may be heralded by a monocytosis with a "shift to the left" in the granulocytes and is usually complete within the ensuing two weeks. Although profound leukopenia and granulocytopenia have been induced in some patients by nitrogen mustard compounds, the "agranulocytic syndrome" with indolent and serious infections has not been reported. This is, no doubt, attributable in part to the prophylactic use of penicillin, blood transfusions and other supportive measures; however, equally important is the fact that bone marrow function returns promptly. Pent-

nucleotide, ferrous adenylate, leukocytic extracts, folic acid and whole blood have not hastened marrow recovery.²⁵⁹

Variable degrees of thrombocytopenia are seen during the third week after a course of therapy, occasionally progressing to low levels with purpura, impaired clot retraction and prolonged bleeding times. A return of platelets to normal levels within the ensuing seven to ten days is the rule. Recently a coagulation defect characterized by prolonged clotting time has been described in some patients and in experimental animals two weeks following nitrogen mustard administration.²⁸² The evidence indicates that this may be due to hyperheparinemia inasmuch as it can be quickly corrected by parenteral injection of toluidine blue or protamine.

A slight fall in hemoglobin, rarely exceeding 1 Gm. per cent, and a decrease in red blood cell count with concomitant depression of reticulocytes may be seen during the first two weeks after a course of treatment, and occasionally a rise in reticulocytes can be detected two to three weeks post-therapy. These findings are of little clinical consequence, however, since an improvement in pre-existent anemia is common in patients responding favorably to the nitrogen mustards.

Bone Marrow—Serial studies of bone marrow have demonstrated cytotoxic effects of the mustard compounds on both mature and immature elements, with progression to almost total aplasia at high dosage levels. The extreme importance of this observation must be borne in mind when successive courses of therapy are initiated. No cumulative effects on the marrow have been reported in those patients in whom sufficient time for complete marrow regeneration has elapsed between courses of nitrogen mustard. Spurr believes that on the basis of his observations recovery cannot be considered complete for six weeks.^{259,260}

Other toxic effects—Studies of hepatic and renal function have disclosed no evidence of toxic effects on these organs following HN therapy.

cases of chronic leukemia, inoperable carcinoma of the lung of anaplastic histology and mycosis fungoides. To say that these are the drugs or treatments of choice is not justified according to available evidence. Such factors as degree of dissemination, with or without obstructive phenomena from tumor masses, refractiveness to other forms of therapy and level of peripheral blood cell values will, in the final appraisal of the patient, dictate the course of action to be taken.

In acute leukemias, squamous cell carcinoma of the lung, carcinoma of the oral cavity, gastrointestinal and genito-urinary tracts, central nervous system tumors and most types of sarcomas not included in the preceding categories little or no justification for mustard chemotherapy exists. In the case of acute leukemias, regardless of cell type, use of these drugs may accelerate the progress of the disease to an earlier fatal termination on the basis of some reports.²⁵³

An intermediate group of conditions exists, including multiple myeloma, neuroblastomas, Ewing's tumor of bone, lymphoepithelioma (Schmincke tumor) and Bock's sarcoid, in which further clinical trial is needed to appraise the merits of alkylamine therapy. In this connection it can be said that a therapeutic trial may be the only means of determining the efficacy of these compounds in a given patient, and certainly there should be no hesitation in offering this group of patients the chance of effective palliative measures when usual ones have failed.

Future developments in the field of tumor chemotherapy will undoubtedly change this picture since an enormous number of related alkylamines remain untried clinically or in the laboratory. The ideal drug would exhibit no toxic side actions and would possess cytotoxic effects confined to pathologic tissue. None such has yet been found.

CONCLUSION

The foregoing presentation did not include all of the chemical agents currently employed in the treatment of malignant

disease. Karnofsky's recent review includes a number of agents not discussed herein.²⁸⁶ Notably omitted from the discussion was the radioactive isotope group of drugs. These agents have contributed and undoubtedly will increasingly contribute significantly to the therapy of cancer. However, since they constitute a specialized form of radiotherapy, they were considered to be outside the scope of this paper.

From the survey which has been made it is possible to draw certain specific conclusions. It is believed that the available evidence warrants the following applications of cancer chemotherapy in medical practice: (1) androgen control therapy of prostatic malignancy when the neoplasm has extended beyond the confines of the gland; (2) urethane in the therapy of chronic myeloid and lymphatic leukemia when radiotherapy is not available or is contraindicated; (3) nitrogen mustard therapy of disseminated malignant lymphomas either as an adjunct to radiotherapy or as an alternate form of therapy.

It is further believed that the following agents merit trial after conventional therapy has proved without avail: (1) androgenic hormone in carcinoma of the breast with skeletal metastases and (2) stilbamidine in multiple myeloma in the presence of intractable pain.

Finally, it is our belief that (1) there is no objective indication that antireticular cytotoxic serum and pteroyltriglutamic acid (teropterin) have any effect on malignant disease and they should therefore not be employed; (2) use of estrogen in the therapy of carcinoma of the breast with soft tissue metastases in postmenopausal women has not been sufficiently explored to recommend its general employment; (3) products of micro-organisms have real potentialities as carcinolytic agents but their value in the therapy of human neoplastic disease has not been demonstrated up to the present.

It is apparent that there are severe limitations to the chemotherapy of cancer at this time. None of the agents discussed has cured cancer and in most instances the

beneficial effects have been relatively transient. Frequently, these facts are interpreted as conclusive evidence that the cure of disseminated malignant disease presents a hopeless problem. This would appear to be a superficial evaluation for the fact remains that several of the drugs which have been discussed destroy malignant cells without destroying the host. To reconcile this undeniable evidence with the observation that only remissions and not cures are produced by chemotherapy in malignant disease is not easy. One explanation which is compatible with the facts is that among the cells of a susceptible tumor there is variation in resistance to the cytotoxic agent which may be a primary or an acquired characteristic. This would be analogous to the situation encountered in infection when micro-organisms become resistant to chemotherapeutic drugs. The problem of drug-resistant micro-organisms has been largely overcome by utilizing several effective antimicrobial agents either simultaneously or in alternate therapeutic courses. When it is recalled that androgen control therapy of prostatic malignancy, urethane and nitrogen mustards have all been developed within the past seven years, it does not seem unreasonable to anticipate additional potent carcinolytic agents in the not too distant future. With an enlarged therapeutic armamentarium, the possibilities for a combined attack on malignant disease offer an attractive and hopeful prospect.

REFERENCES

1. ACKERMAN, L. V. and DEL REGATO, J. A. *Cancer*. St. Louis, 1947. C. V. Mosby Co.
2. SIMPSON, W. M. Progress in cancer research. *Am. J. Clin. Path.*, 17: 513, 1947.
3. BUSCH, W. VI. Verhandlungen ärztlicher Gesellschaften. *Berl. klin. Wchnschr.*, 3: 245, 1866.
4. FEHLEISEN. Ueber die Züchtung der Erysipelkokken auf künstlichen Nährboden und ihre Uebertragbarkeit auf den Menschen. *Deutsche med. Wchnschr.*, 8: 553, 1882.
5. SPRONCK, C. H. H. Tumeurs malignes et maladies infectieuses. *Ann. Inst. Pasteur*, 6: 683, 1892.
6. BEEBE, S. P. and TRACY, M. The treatment of experimental tumors with bacterial toxins. *J. A. M. A.*, 49: 1493, 1907.
7. GRATIA, A. and LINZ, R. Le phénomène de Shwartzman dans le sarcome du cobaye. *Compt. rend. Soc. de biol.*, 108: 427, 1931.
8. SHWARTZMAN, G. and MICHAÏLOVSKY, N. Phenomenon of local skin reactivity to bacterial filtrates in treatment of mouse sarcoma 180. *Proc. Soc. Exper. Biol. & Med.*, 29: 737, 1932.
9. SHEAR, M. J. and ANDERVONT, H. B. Annual report of the Surgeon General of the Public Health Service of the U. S. Washington, D. C., 1932.
10. SHEAR, M. J. Studies on the chemical treatment of tumors. II. The effect of disturbances in fluid exchange on transplanted mouse tumors. *Am. J. Cancer*, 25: 66, 1935.
11. ANDERVONT, H. B. The reaction of mice and of various mouse tumors to the injection of bacterial products. *Am. J. Cancer*, 27: 77, 1936.
12. SHEAR, M. J. and TURNER, F. C. Studies on the chemical treatment of tumors. v. Separation of the hemorrhage-producing fraction from *Bacillus prodigiosus* filtrates. *J. Biol. Chem.*, 133: 87, 1940.
13. IDEM. Studies on the chemical treatment of tumors. v. Isolation of the hemorrhage-producing fraction from *Serratia marcescens* (*Bacillus prodigiosus*) culture filtrate. *J. Nat. Cancer Inst.*, 4: 81, 1943.
14. SHEAR, M. J., PERRAULT, A. and ADAMS, J. R., JR. Chemical treatment of tumors. VI. Method employed in determining the potency of hemorrhage-producing bacterial preparations. *J. Nat. Cancer Inst.*, 4: 99, 1943.
15. HARTWELL, J. L., SHEAR, M. J. and ADAMS, J. R., JR. VII. Nature of the hemorrhage-producing fraction from *Serratia marcescens* (*Bacillus prodigiosus*) culture filtrate. *J. Nat. Cancer Inst.*, 4: 107, 1943.
16. SHEAR, M. J. Chemical treatment of tumors. IX. Reactions of mice with primary subcutaneous tumors to injection of hemorrhage-producing bacterial polysaccharide. *J. Nat. Cancer Inst.*, 4: 461, 1944.
17. DAELS, F. Beitrag zum Studium des Antagonismus zwischen den Karzinom-, Spirillen- und Trypanosomeninfektionen. *Arch. f. Hyg.*, 72: 257, 1910.
18. COMSIA, O. L'antagonisme entre la spirochetose recurrente et le cancer expérimental chez les souris. *Compt. rend. Soc. de biol.*, 99: 900, 1928.
19. ROSKIN, G. and EXAMPLIARSKAIA, E. Protozoeninfektion und experimenteller Krebs. *Ztschr. f. Krebsforsch.*, 34: 628, 1931.
20. ROSKIN, G. Toxin therapy of experimental cancer; the influence of protozoan infections upon transplanted cancer. *Cancer Research*, 6: 363, 1946.
21. ROSKIN, G. Toxin therapy of experimental cancer. *Am. Rev. Soviet Med.*, 4: 111, 1946.
22. MALISOFF, W. M. The action of the endotoxin of *Trypanosoma cruzi* (KR) on malignant mouse tumors. *Science*, 106: 591, 1947.
23. HAUSCHKA, T. S. Sex of host as a factor in Chagas' disease. *J. Parasitol.*, 33: 399, 1947.
24. HAUSCHKA, T. S. *Trypanosoma cruzi* "endotoxin" in the treatment of mouse tumors. Abstracts of 4th Internat. Cancer Research Congress. P. 89. September, 1947.
25. HAUSCHKA, T., SAXE, L. H., JR. and BLAIR, M. *Trypanosoma cruzi* in the treatment of mouse tumors. *J. Nat. Cancer Inst.*, 7: 189, 1947.

26. HAUSCHKA, T. S. and GOODWIN, M. B. Trypanosoma cruzi endotoxin (KR) in the treatment of malignant mouse tumors. *Science*, 107: 600, 1948.
27. COHEN, A. L., BORSOOK, H. and DUBNOFF, J. W. The effect of a sparsarcina ureac preparation on tumor cells *in vitro*. *Proc. Soc. Exper. Biol. & Med.*, 66: 440, 1947.
28. ARTHUS, M. Injections répétées de serum de cheval chez le lapin. *Compt. rend. Soc. de biol.*, 55: 817, 1903.
29. WILSON, G. S. and MILES, A. A. Topley and Wilson's Principles of Bacteriology and Immunity. Baltimore, 1946. Williams & Wilkins Co.
30. SHWARTZMAN, G. A new phenomenon of local skin reactivity to B. typhosus culture filtrate. *Proc. Soc. Exper. Biol. & Med.*, 25: 560, 1927-1928.
31. HANGER, F. M., JR. Effect of intravenous bacterial filtrates on skin tests and local infections. *Ibid.*, 25: 775, 1927-1928.
32. SHWARTZMAN, G. Phenomenon of Local Tissue Reactivity. New York, 1937. Paul B. Hoeber, Inc.
33. DURAN-REYNALS, F. Reaction of transplantable and spontaneous tumors to blood-carried bacterial toxins in animals unsusceptible to the Shwartzman phenomenon. *Proc. Soc. Exper. Biol. & Med.*, 31: 341, 1933.
34. APITZ, K. Über Blutungsreaktionen im Impfcarcinom der Maus. *Ztschr. f. Krebsforsch.*, 40: 50, 1933.
35. SHEAR, M. J. Studies on the chemical treatment of tumors. II. The effect of disturbances in fluid exchange on transplanted mouse tumors. *Am. J. Cancer*, 25: 66, 1935.
36. DURAN-REYNALS, F. Reaction of spontaneous mouse carcinoma to blood-carried bacterial toxins. *Proc. Soc. Exper. Biol. & Med.*, 32: 1517, 1935.
37. COLEY, W. B. Contribution to the knowledge of sarcoma. *Ann. Surg.*, 14: 199, 1891.
38. IDEM. The diagnosis and treatment of bone sarcoma. *Glasgow M. J.*, 126: 49, 1936.
39. NAUTS, H. C., SWIFT, W. E. and COLEY, B. L. The treatment of malignant tumors by bacterial toxins as developed by the late William B. Coley, M.D., reviewed in the light of modern research. *Cancer Research*, 6: 205, 1946.
40. TRACY, M. A study of the toxins of Bacillus prodigiosus. *J. M. Research*, 16: 307, 1907-1908.
41. FOWLER, G. R. The use of animal toxins in the treatment of inoperable malignant tumors. *Am. J. M. Sc.*, 116: 161, 1898.
42. BRUES, A. M. and SHEAR, M. J. Chemical treatment of tumors. x. Reactions of four patients with advanced malignant tumors to injection of a polysaccharide from Serratia marcescens culture filtrate. *J. Nat. Cancer Inst.*, 5: 195, 1944.
43. HOLLOMAN, A. L. Reactions of patients and of tumors to injection of S. marcescens polysaccharide in eight cases of malignant disease. P. 273. Approaches to Tumor Chemotherapy. American Association for the Advancement of Science, 1947.
44. O'KEY, R. Reactions of patients to injection of S. marcescens polysaccharide in nine further cases of malignant disease. P. 277. Approaches to Tumor Chemotherapy. American Association for the Advancement of Science, 1947.
45. KLYUEVA, N. G. Paths of cancer biotherapy. *Am. Rev. Soviet Med.*, 4: 408, 1947.
46. STERN, K. and WILLHEIM, R. The Biochemistry of Malignant Tumors. Chapt. 8. Reference Press, 1943.
47. BABES, A. La rate chez les lapins avec cancer du goudron. *Bull. Assoc. franc. p. l'étude du cancer*, 19: 232, 1930.
48. TWORT, J. M. and LASNITZKI, M. Studies on the pituitary weight of rats inoculated with a transmissible tumor. *Endocrinology*, 23: 87, 1938.
49. BROWN, W. H. and PEARCE, L. The reaction of the endocrine system of the rabbit to tumor inoculation and the relation of this reaction to malignancy. *Proc. Soc. Exper. Biol. & Med.*, 20: 472, 1923.
50. SURE, B., THEIS, R. M. and HARRELSON, R. T. Influence of Walker carcinosarcoma on concentration of ascorbic acid in various endocrines and organs. *Am. J. Cancer*, 36: 252, 1939.
51. ROFFO, A. H. Eine biologische Reaktion der Milz, hervorgerufen durch blutunverträglichkeitstesteten Ratten. *Ztschr. f. Krebsforsch.*, 30: 180, 1929.
52. BEARD, H. H., HALPERIN, B. and LIBERT, S. A. Effect of intraperitoneal injection of malignant urine extracts in normal and hypophysectomized rats. *Science*, 105: 475, 1947.
53. FLANTCHIK, L. I. Morphological and biological characteristics of cancer metastasis in the spleen. *Am. J. Cancer*, 31: 152, 1937.
54. ANDERVONT, H. B. The influence of trypan blue upon the resistance of mice to transplantable and induced tumors. *Pub. Health Rep.*, 51: 591, 1936.
55. KHALETZAYA, F. M. The influence of splenectomy upon the development of tumors induced by chemical agents. *Am. J. Cancer*, 40: 262, 1940.
56. LATTI, J. S. and JOHNSON, H. N. Studies of lymphatic tissue grown *in vitro* with splenic extract as culture medium. *Arch. f. exper. Zellforsch.*, 16: 221, 1934.
57. JONES, L. O. *In vitro* studies on the effect of spleen, striated muscle, and kidney upon the growth of sarcoma 180 and mammary carcinoma in mice. *Cancer Research*. (In press.)
58. BOGOLOMETZ, A. A. Anti-reticular cytotoxic serum as a means of pathogenetic therapy. *Am. Rev. Soviet Med.*, 1: 101, 1943.
59. STRAUS, R. Studies on anti-reticular cytotoxic serum. I. Introduction and review of the literature. *J. Immunol.*, 54: 151, 1946.
60. FEDYUSHIN, M. P. The experimental application of anti-reticular cytotoxic serum in cancer cases. Quoted by Straus, R.⁵⁹
61. STRAUS, R., RUNJAVAC, M., ZAITLIN, R., DUBOFF, G. and SWERDLOW, H. Studies on anti-reticular cytotoxic serum. II. Preparation and titration of the serum and study of its serological properties. *J. Immunol.*, 54: 155, 1946.
62. STRAUS, R., HORWITZ, M., LEVINTHAL, H., COHEN, A. L. and RUNJAVAC, M. Studies on anti-reticular cytotoxic serum. III. Effect of ACS on the healing of experimentally produced fractures in rabbits. *J. Immunol.*, 54: 163, 1946.
63. MARCHUK, P. D. A method of preparing and pre-

- serving anti-reticular cytotoxic serum. *Am. Rev. Soviet Med.*, 1: 113, 1943-1944.
64. DAVIS, W. D., JR. Clinical observations in patients treated with anti-reticular cytotoxic serum. Preliminary report. Meet., Am. Fed. Clin. Research. April 8, 1947. *Am. J. Med.*, 3: 123, 1947.
 65. FRIEDMAN, R. and STRITZLER C. Mycosis fungoides resisting treatment with both nitrogen mustard and anti-reticular cytotoxic serum. *J. Invest. Dermat.* 10: 227, 1948.
 66. SKAPIER, J. Therapeutic use of anti-reticular cytotoxic serum (ACS) in Hodgkin's disease. *Cancer Research*, 7: 369, 1947.
 67. ROGOFF, B., FREYBERG, R. H., POWELL, H. M. and RICE, R. M. Experiences with antireticular cytotoxic serum (ACS) in arthritis. *Am. J. M. Sc.*, 214: 395, 1947.
 68. WATSON, G. F., DILLER, I. C. and LUDWICK, N. V. Spleen extract and tumor growth. *Science*, 106: 348, 1947.
 69. LEWISOHN, R. Effect of subcutaneous injections of concentrated spleen extract on mouse sarcoma 180. *Surg. Gynec., & Obst.*, 66: 563, 1938.
 70. LEWISOHN, R. Chemotherapeutic regressions of transplanted and spontaneous cancers in mice. 1. Review of the work of the laboratory 1937-1945. Approaches to Tumor Chemotherapy. P. 139. American Association for the Advancement of Science, 1947.
 71. LEUCHTENBERGER, C., LEWISOHN, R., LAZLO, D. and LEUCHTENBERGER, R. "Folic acid" a tumor growth inhibitor. *Proc. Soc. Exper. Biol. & Med.*, 55: 204, 1944.
 72. LEUCHTENBERGER, R., LEUCHTENBERGER, C., LAZLO, D. and LEWISOHN R. The influence of "folic acid" on spontaneous breast cancers in mice. *Science*, 101: 46, 1945.
 73. LEUCHTENBERGER, C. Results of treatment of spontaneous tumors with "folic acid" and allied substances. Approaches to Tumor Chemotherapy. P. 157. American Association for the Advancement of Science, 1947.
 74. SUGIURA, K. Effect of intravenous injection of yeast and barley extracts and L. casei factor upon spontaneous mammary adenocarcinoma in mice. Approaches to Tumor Chemotherapy. P. 208. American Association for the Advancement of Science, 1947.
 75. BURK, D. A discussion of C. Leuchtenberger's paper.⁷³
 76. MORRIS, H. P. A discussion of Leuchtenberger's paper.⁷³
 77. FARBER, S., CUTLER, E. C., HAWKINS, J. W., HARRISON, J. H., PIERCE, E. C. and LENZ, G. G. The Action of pteroylglutamic conjugates on man. *Science*, 106: 619, 1947.
 78. KLAINER, M. J. A case report of metastatic carcinoma treated with teropterin. *Tr. New York Acad. Sc.*, 10: 71, 1948.
 79. LEHV, S. P., WRIGHT, L. T., WEINTRAUB, S. and ARONS, I. Use of teropterin in neoplastic disease: a preliminary clinical report. *Tr. New York Acad. Sc.*, 10: 75, 1948.
 80. MEYER, L. M. Use of folic acid derivatives in the treatment of human leukemia. *Tr. New York Acad. Sc.*, 10: 99, 1948.
 81. WELCH, A. D. The present status of pteroylglutamic acid and of other hematopoietic agents. *Federation Proc.*, 6: 471, 1947.
 82. WOLL, E. The Rous chicken sarcoma in birds treated with folic acid and its derivatives: a pathological study. *Tr. New York Acad. Sc.*, 10: 83, 1948.
 83. LITTLE, P. A., SAMPATH, A., PAGANELLI, V., LOCKE, E. and SUBBAROW, Y. The effect of folic acid and its antagonists on Rous chicken sarcoma. *Tr. New York Acad. Sc.*, 10: 91, 1948.
 84. Council on Pharmacy and Chemistry. "Teropterin" and "diopterin" in the treatment of cancer. *J. A. M. A.*, 137: 699, 1948.
 85. WOOLEY, D. W. Recent advances in study of biological competition between structurally related compounds. *Physiol. Rev.*, 27: 308, 1947.
 86. HUTCHINGS, B. L. Pteroylaspartic acid an antagonist for pteroylglutamic acid. *J. Biol. Chem.*, 170: 323, 1947.
 87. SEEGER, D. R., SMITH, J. M., JR. and HULTQUIST, M. E. Antagonist for pteroylglutamic acid. *J. Am. Chem. Soc.*, 69: 2567, 1947.
 88. FARBER, S., DIAMOND, L. K., MERCER, R. D., SYLVESTER, R. F. and WOLFF, J. A. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroylglutamic acid (aminopterin). *New England J. Med.*, 238: 787, 1948.
 89. FARBER, S. Papers presented at the International Congress of Hematology, Buffalo, August, 1948 and the American Cancer Society meetings, New York, November, 1948.
 90. DAMESHEK, WM. The use of folic acid antagonists in acute leukemia. *Blood*, 3: 1057, 1948.
 91. STRONG, R. P. Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases. Philadelphia, 1944. The Blakiston Co.
 92. YORKE, W. Recent work on chemotherapy of protozoal infections. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 33: 463, 1940.
 93. ADAMS, A. R. D. and YORKE, W. Studies in chemotherapy. xxiii. A case of Indian kala-azar treated with 4:4'-diamidino stilbene. *Ann. Trop. Med.*, 33: 323, 1939.
 94. SNAPPER, I. On the influence of stilbamidine upon multiple myeloma. *J. Mt. Sinai Hosp.*, 13: 119, 1946.
 95. SNAPPER, I. Stilbamidine and pentamidine in multiple myeloma. *J. A. M. A.*, 133: 157, 1947.
 96. SNAPPER, I. and SCHNEID, B. On the influence of stilbamidine upon myeloma cells. *Blood*, 1: 534, 1946.
 97. SNAPPER, I., MIRSKY, A. E., RIS, H., SCHNEID, B. and ROSENTHAL, M. Development of inclusion bodies containing ribose nucleic acid in myeloma cells after injections of stilbamidine. Determination of stilbamidine in myeloma tissue. *Blood*, 2: 311, 1947.
 98. KOPAC, M. J. Cellular mechanisms in chemotherapy. *Tr. New York Acad. Sc.*, 8: 5, 1945.
 99. EISEN, M. J. Transplantable carcinoma of the rat breast. *Am. J. Cancer*, 39: 36, 1940.
 100. MURPHY, J. B. and STURM, E. The transmission of

- an induced lymphatic leukemia and lymphosarcoma in the rat. *Cancer Research*, 1: 379, 1941.
101. SNAPPER, I. Treatment of multiple myeloma with "stilbamidine." Clinical results and morphologic changes. *J. A. M. A.*, 137: 513, 1948.
 102. FULTON, J. D. and YORKE, W. xxxi. The increased toxicity of old solutions of stilbamidine. *Ann. Trop. Med.*, 36: 134, 1942.
 103. ARAI, H. and SNAPPER, I. The influence of stilbamidine upon kidney function, liver function and peripheral blood in multiple myeloma. Neurologic sequelae of stilbamidine therapy. *New York State J. Med.*, 47: 1867, 1947.
 104. NAPIER, L. E. and SEN GUPTA, P. C. A peculiar neurological sequel to administration of 4:4'-diamidino-diphenyl-ethylene. *Indian M. Gaz.*, 77: 71, 1942.
 105. SEN GUPTA, P. C. Observations of the neuropathic sequel of diamidinostilbene therapy in kala-azar. *Ibid.*, 78: 537, 1943.
 106. KIRK, R. and HENRY, A. J. Observations on the toxicity of stilbamidine. *Ann. Trop. Med.*, 38: 99, 1944.
 107. OASTLER, E. G. and FIDLER, H. K. Cerebral lesions produced in healthy dogs by the intravenous injection of 4:4'-diamidino stilbene. *Tr. Roy. Soc. Trop. Med.*, 39: 533, 1946.
 108. RUBINSTEIN, M. A. Chemotherapy of multiple myeloma: the use of antimony. *Blood*, 2: 555, 1947.
 109. LING, S. M. Distribution of protein fractions in the serum of kala-azar patients. *Proc. Soc. Exper. Biol. & Med.*, 27: 247, 1930.
 110. GUTMAN, A. B., MOORE, D. H., GUTMAN, E. B., MCCLELLAN, V. and KABAT, E. A. Fractionation of serum proteins in hyperproteinemia with special reference to multiple myeloma. *J. Clin. Investigation*, 20: 765, 1941.
 111. MOORE, D. H., KABAT, E. A. and GUTMAN, A. B. Bence-Jones proteinemia in multiple myeloma. *J. Clin. Investigation*, 22: 67, 1943.
 112. HADDOW, A. and SEXTON, W. A. Influence of carbamic esters (urethanes) on experimental animal tumors. *Nature, London*, 157: 500, 1946.
 113. CLARK, A. J. Mode of Action of Drugs on Cells. London, 1933.
 114. QUASTEL, J. H. Effects of narcotics and benzedrine on metabolic processes in the central nervous system. *Tr. Faraday Soc.*, 39: 348, 1943.
 115. JOHNSON, F. H., EYRING, H., STEBLAY, R., CHAPLIN, H., HUBER, C. and GHERARDI, G. The nature and control of reactions in bioluminescence. *J. Gen. Physiol.*, 28: 463, 1945.
 116. PLENTL, A. A. and SCHOENHEIMER, R. Studies in the metabolism of purines and pyrimidines by means of isotopic nitrogen. *J. Biol. Chem.*, 153: 203, 1944.
 117. PATERSON, E., HADDOW, A., AP THOMAS, M. I. R., and WATKINSON, J. M. Leukemia treated with urethane compared with deep x-ray therapy. *Lancet*, 1: 677, 1946.
 118. MURPHY, J. B. and STURM, E. The effect of urethane on lymphatic leukemia in rats. *Science*, 104: 386, 1947.
 119. ENGSTROM, R. M., KIRSCHBAUM, A. and MIXER, H. W. Effect of urethane on mouse myelogenous leukemia. *Science*, 105: 255, 1947.
 120. WEIR, D. R. and HEINLE, R. W. Effect of urethane on transplanted leukemia of Ak mice. *Proc. Soc. Exper. Biol. & Med.*, 66: 268, 1947.
 121. LAW, L. W. Effect of urethane on a transplantable acute lymphoid leukemia. *Proc. Soc. Exper. Biol. & Med.*, 66: 158, 1947.
 122. SKIPPER, H. E., RISER, W. H., JR., STELZENMULLER, A. and HOLT, H. Carbamates in the chemotherapy of leukemia. *Blood*, 3: 774, 1948.
 123. WATKINS, C. H. Evaluation of therapeutic agents in recent use in the control of experimental and human leukemia. *Proc. Inst. Med. Chicago*, 16: 386, 1947.
 124. CRESKOFF, A. J., FITZ-HUGH, T. and FROST, J. W. Urethane therapy in leukemia. *Blood*, 3: 896, 1948.
 125. HIRSCHBOECK, J. S., LINDERT, M. C. F., CHASE, F. and CALVEY, T. L. Effects of urethane in the treatment of leukemia and metastatic malignant tumors. *J. A. M. A.*, 136: 90, 1948.
 126. WATKINS, C. H., COOPER, T. and GRIFFIN, H. Z. The use of urethane (ethylcarbamate) in the treatment of leukemia. *Blood*, 3: 892, 1948.
 127. MCALISTER, J. P. Leukemia treated with urethane. *Arkansas M. Soc. J.*, 44: 139, 1947.
 128. BERMAN, L. and AXELROD, A. R. Effect of urethane on malignant diseases. Clinical, hematologic and histologic observations on patients with carcinoma, leukemia and related diseases. *Am. J. Clin. Path.*, 18: 104, 1948.
 129. GOODMAN, M. J. and LEWIS, H. P. Urethane in leukemia. *J. A. M. A.*, 132: 1105, 1946.
 130. HUGGINS, C., YU, S. T. and JONES, R., JR. Inhibitory effects of ethyl carbamate on prostatic cancer. *Science*, 106: 147, 1947.
 131. WEBSTER, J. J. Urethane in leukemia. *J. A. M. A.*, 135: 901, 1947.
 132. CIVIALE, quoted by White, J. W. The present position of the surgery of the hypertrophied prostate. *Ann. Surg.*, 18: 152, 1893.
 133. HUGGINS, C., MASINA, M. H., EICHELBERGER, L. and WHARTON, J. D. Quantitative studies of prostatic secretion. I. Characteristics of the normal secretion; the influence of thyroid, suprarenal and testis extirpation and androgen substitution on the prostatic output. *J. Exper. Med.*, 70: 543, 1939.
 134. HUGGINS, C. and STEVENS, R. A. The effect of castration on benign hypertrophy of the prostate in man. *J. Urol.*, 43: 705, 1940.
 135. KUTSCHER, W. and WOLBERGS, H. Prostataphosphatase. *Ztschr. f. physiol. Chem.*, 236: 237, 1935.
 136. GUTMAN, A. B. and GUTMAN, E. B. An "acid" phosphatase occurring in the serum of patients with metastasizing carcinoma of the prostate gland. *J. Clin. Investigation*, 17: 473, 1938.
 137. SULLIVAN, T. J., GUTMAN, E. B. and GUTMAN, A. B. Theory and application of the serum "acid" phosphatase determination in metastasizing prostatic carcinoma; early effects of castration. *J. Urol.*, 48: 426, 1942.
 138. GOMORI, G. Distribution of acid phosphatase in the tissues under normal and under pathological conditions. *Arch. Path.*, 32: 189, 1941.

139. HUGGINS, C. and HODGES, C. V. Studies on prostatic cancer. i. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Research*, 1: 293, 1941.
140. HUGGINS, C., STEVENS, R. E. and HODGES, C. V. Studies on prostatic cancer. ii. The effects of castration on advanced carcinoma of the prostate gland. *Arch. Surg.*, 43: 209, 1941.
141. GUTMAN, E. B., SPROUL, E. E. and GUTMAN, A. B. Significance of increased phosphatase activity of bone at site of osteoplastic metastases secondary to carcinoma of the prostate gland. *Am. J. Cancer*, 28: 485, 1936.
142. SMITH, P. E. and ENGLE, E. T. Experimental evidence regarding the role of the anterior pituitary in the development and regulation of the genital system. *Am. J. Anat.*, 40: 159, 1927.
143. MOORE, C. R. and PRICE, D. The question of sex hormone antagonism. *Proc. Soc. Exper. Biol. & Med.*, 28: 38, 1930.
144. HUGGINS, C. and CLARK, P. J. Quantitative studies of prostatic secretion. ii. The effect of castration and of estrogen injection on the normal and on the hyperplastic prostatic glands of dogs. *J. Exper. Med.*, 72: 747, 1940.
145. DEAN, A. L. Carcinoma of the prostate. *Bull. New York Acad. Med.*, 23: 454, 1947.
146. CORI, C. F. Enzymatic reactions in carbohydrate metabolism. Harvey Lectures, 41: 253, 1945-1946.
147. BARRON, E. S. G. and HUGGINS, C. The metabolism of isolated prostatic tissue. *J. Urol.*, 51: 630, 1944.
148. HERBST, W. P. The effects of estradiol dipropionate and diethyl stilbestrol on malignant prostatic tissue. *Tr. Am. A. Genito-Urin. Surgeons*, 34: 195, 1941.
149. KAHLE, P. J., OGDEN, H. D., JR. and GETZOFF, P. L. The effect of diethylstilbestrol and diethylstilbestrol dipropionate on carcinoma of the prostate gland. *J. Urol.*, 48: 83, 1942.
150. HECKEL, N. J. and KRETSCHMER, H. L. Carcinoma of the prostate treated with diethylstilbestrol. Histologic alterations. *J. A. M. A.*, 119: 1087, 1942.
151. CHUTE, R. and WILLETTTS, A. T. The treatment of cancer of the prostate with castration and the administration of estrogen. A preliminary report. *New England J. Med.*, 227: 863, 1942.
152. DEAN, A. L., WOODARD, H. Q. and TWOMBLY, G. H. The endocrine treatment of cancers of the prostate gland. *Surgery*, 16: 169, 1944.
153. FERGUSON, J. D. and PAGEL, W. Some observations on carcinoma of the prostate treated with oestrogens as demonstrated by serial biopsies. *Brit. J. Surg.*, 33: 122, 1945.
154. FERGUSON, J. D. Carcinoma of the prostate treated with oestrogens. *Lancet*, 251: 551, 1946.
155. MCCREA, L. E. Carcinoma of the prostate: a resume of treatment with ethinyl estradiol; preliminary report. *J. Urol.*, 56: 697, 1946.
156. HECKEL, N. J. Sex hormone therapy in the treatment of carcinoma of the prostate and benign prostatic hypertrophy. *Clinics*, 5: 860, 1946.
157. MATHÉ, C. P. and ARDILA, C. E. Carcinoma of the prostate. Review of 130 cases treated between 1940 and 1946. *Surg., Gynec. & Obst.*, 84: 276, 1947.
158. DEMING, C. L. Present evaluation of the response of prostatic cancer to hormone therapy. *South. M. J.*, 40: 328, 1947.
159. COLSTON, J. A. C. and BRENDLER, H. Endocrine therapy in carcinoma of the prostate. Preparation of patients for radical prostatectomy. *J. A. M. A.*, 134: 848, 1947.
160. BUCHERT, W. I., CULP, D. A. and JONES, G. H. Carcinoma of the prostate gland. An analysis of 135 consecutive cases. *Pennsylvania M. J.*, 51: 165, 1947.
161. SCHENKEN, J. R., BURNS, E. L. and KAHLE, P. J. The effect of diethylstilbestrol and diethylstilbestrol dipropionate on carcinoma of the prostate gland. ii. Cytologic changes following treatment. *J. Urol.*, 48: 99, 1942.
162. SCHWARTZ, M. The effect of stilbestrol on the testis and breast of patients treated for carcinoma of the prostate gland. *Proc. Am. Federation Clin. Research*, 2: 97, 1945.
163. MOORE, G. F., WATTENBERG, C. A. and ROSE, D. K. Breast changes due to diethylstilbestrol during treatment of cancer of the prostate gland. *J. A. M. A.*, 127: 60, 1945.
164. ABRAMSON, W. and WARSHAWSKY, H. Cancer of the breast in the male secondary to estrogenic administration. Report of a case. *J. Urol.*, 59: 76, 1948.
165. HAAGENSEN, C. D. Personal communication.
166. THORN, G. W., NELSON, K. R. and THORN, D. W. A study of the mechanism of edema associated with menstruation. *Endocrinology*, 22: 155, 1938.
167. BLAND, E. F. and NATHANSON, I. T. Personal communication.
168. BUMPUS, H. C., JR. Carcinoma of the prostate. A clinical study of 1,000 cases. *Surg., Gynec. & Obst.*, 43: 150, 1926.
169. HOVENIAN, M. S. and DEMING, C. L. The heterologous growth of cancer of the human prostate. *Surg., Gynec. & Obst.*, 86: 29, 1948.
170. LATHROP, A. E. C. and LOEB, L. Further investigations on the origin of tumors in mice. iii. On the part played by internal secretion in the spontaneous development of tumors. *J. Cancer Research*, 1: 1, 1916.
171. LOEB, L. Further investigations on the origin of tumors in mice. vi. Internal secretion as a factor in the origin of tumors. *J. M. Research*, 40: 477, 1919.
172. LACASSAGNE, A. Hormonal pathogenesis of adenocarcinoma of the breast. *Am. J. Cancer*, 27: 217, 1936.
173. LACASSAGNE, A. Tentatives pour modifier par la progestérone ou par la testostérone, l'apparition des adénocarcinomes mammaires provoqués par l'oestroné chez la souris. *Compt. rend. Soc. de biol.*, 126: 385, 1937.
174. LACASSAGNE, A. Adénocarcinome mammaire de la souris et hormones mâles. *Bull. Assoc. franc. p. l'étude du cancer*, 28: 951, 1939.
175. NATHANSON, I. T. and ANDERVONT, H. B. Effect of testosterone propionate on development and growth of mammary carcinoma in female mice. *Proc. Soc. Exper. Biol. & Med.*, 40: 421, 1939.

176. LOESER, A. A. Mammary carcinoma. Response to implantation of male hormone and progesterone. *Lancet*, 2: 698, 1941.
177. ULRICH, P. Testosterone (hormone mâle) et son rôle possible dans le traitement de certains cancers du sein. *Acta, Union internat. contre cancer*, 4: 377, 1939.
178. FELS, E. Treatment of breast cancer with testosterone propionate. A preliminary report. *J. Clin. Endocrinol.*, 4: 121, 1944.
179. ALLEN, E. Sex and Internal Secretions. Baltimore, 1939. Williams & Wilkins Co.
180. MACBRYDE, C. M. The production of breast growth in the human female by the local application of estrogenic ointment. *J. A. M. A.*, 112: 1045, 1939.
181. CORNER, G. W. The Hormones in Human Reproduction. Princeton, 1942. Princeton University Press.
182. RIDDLE, O., BATES, R. W. and DYKSHORN, S. W. The preparation, identification and assay of prolactin—a hormone of the anterior pituitary. *Am. J. Physiol.*, 105: 191, 1933.
183. RIDDLE, O. Lactogenic and mammogenic hormones. Glandular Physiology and Therapy. American Medical Association, Chicago, 1942.
184. GARDNER, W. U. and WHITE, A. Mammary growth in hypophysectomized male mice receiving estrogen and prolactin. *Proc. Soc. Exper. Biol. & Med.*, 48: 590, 1941.
185. REICHSTEIN, T. and SHOPEE, C. W. The hormones of the adrenal cortex. Vitamins and Hormones. Vol. I. New York, 1943. Academic Press, Inc.
186. SALMON, U. J. Effect of testosterone propionate upon gonadotrophic hormone excretion and vaginal smears of human female castrate. *Proc. Soc. Exper. Biol. & Med.*, 37: 488, 1937.
187. LONG, C. N. H. The conditions associated with the secretion of the adrenal cortex. *Federation Proc.*, 6: 461, 1947.
188. SHORR, E., PAPANICOLAOU, G. N. and STIMMEL, B. F. Neutralization of ovarian follicular hormone in women by simultaneous administration of male sex hormone. *Proc. Soc. Exper. Biol. & Med.*, 38: 759, 1938.
189. ROBSON, J. M. Relative effectiveness of testosterone and of progesterone in the inhibition of oestrus and of the vaginal action of oestrin in mice. *J. Physiol.*, 90: 15P, 1937.
190. ALBRIGHT, F. Osteoporosis. *Ann. Int. Med.*, 27: 861, 1947.
191. REIFENSTEIN, E. C., JR. and ALBRIGHT, F. The metabolic effects of steroid hormones in osteoporosis. *J. Clin. Investigation*, 26: 24, 1947.
192. KENYON, A. T., KNOWLTON, K., SANDIFORD, I., KOCH, F. C. and LATWIN, G. A comparative study of the metabolic effects of testosterone propionate in normal men and women and in eunuchoidism. *Endocrinology*, 26: 26, 1940.
193. ABELS, J. C., YOUNG, N. F. and TAYLOR, H. C., JR. Effects of testosterone and of testosterone propionate on protein formation in man. *J. Clin. Endocrinol.*, 4: 198, 1944.
194. FARROW, J. H. and WOODARD, H. Q. The influence of androgenic and estrogenic substances on the serum calcium in cases of skeletal metastases from mammary cancer. *J. A. M. A.*, 118: 339, 1942.
195. HERRMANN, J. B. and ADAIR, F. E. The effect of testosterone propionate on carcinoma of the female breast with soft tissue metastases. *J. Clin. Endocrinol.*, 6: 769, 1946.
196. ADAIR, F. E. and HERRMANN, J. B. The use of testosterone propionate in the treatment of advanced carcinoma of the breast. *Ann. Surg.*, 123: 1023, 1946.
197. HERRMANN, J. B., ADAIR, F. E. and WOODARD, H. Q. The use of testosterone propionate in the treatment of advanced carcinoma of the breast. II. The treatment of osseous metastases. *Surgery*, 22: 101, 1947.
198. ADAIR, F. E. The use of the male sex hormone in women with breast cancer. *Surg., Gynec. & Obst.*, 84: 719, 1947.
199. ADAIR, F. E. Testosterone in the treatment of breast carcinoma. *M. Clin. North America*, January, 1948.
200. SCHWANDER, H. and MARVIN, H. N. Treatment of carcinoma of the human breast with testosterone propionate: a report of five cases. *J. Clin. Endocrinol.*, 7: 423, 1947.
201. JONES, H. W., JR. Testosterone in the treatment of advanced breast cancer. *South. M. J.*, 41: 4, 1948.
202. DAVISON, T. C. and LETTON, A. H. Testosterone in far advanced breast cancer. *South. Surgeon*, 14: 170, 1948.
203. WALKER, J. Z. Discussion on advanced cases of carcinoma of the breast treated by stilboestrol. *Proc. Roy. Soc. Med.*, 37: 731, 1944.
204. HADDOW, A. The influence of carcinogenic compounds and related substances on the rate of growth of spontaneous tumors of the mouse. *J. Path. & Bact.*, 47: 567, 1938.
205. SYMPOSIUM. Discussion on advanced cases of carcinoma of the breast treated by stilboestrol. *Proc. Roy. Soc. Med.*, 37: 731, 1944.
206. HADDOW, A., WATKINSON, J. M., PATERSON, E. and KOLLER, P. C. Influence of synthetic oestrogens upon advanced malignant disease. *Brit. M. J.*, 2: 393, 1944.
207. NATHANSON, I. T. The effect of stilbestrol on advanced cancer of the breast. *Cancer Research*, 6: 484, 1946.
208. HERRMANN, J. B., ADAIR, F. E. and WOODARD, H. Q. Effect of estrogenic hormone on advanced carcinoma of the female breast. *Arch. Surg.*, 54: 1, 1947.
209. MÜLLER, U. Die chemische Waffe in Weltkrieg und Jetzt. Verlag Chemie, Berlin, 1935.
210. PRENTISS, A. M. Chemicals in War. New York, 1937. McGraw-Hill Book Company, Inc.
211. MANDEL, M. and GIBSON, W. S. Clinical manifestations and treatment of gas poisoning. *J. A. M. A.*, 69: 1970, 1917.
212. Editorial. The pathology of "mustard gas." *J. A. M. A.*, 70: 1947, 1918.
213. KRUMBHAAR, E. B. and Krumbhaar, H. D. The blood and bone marrow in yellow cross gas (mustard gas) poisoning. *J. M. Research*, 40: 497, 1919.

214. LYNCH, V., SMITH, H. W. and MARSHALL, E. K., JR. On dichloroethyl sulfide (mustard gas). i. The systemic effects and mechanism of action. *J. Pharmacol. & Exper. Therap.*, 12: 265, 1918-1919.
215. GILMAN, A. and PHILIPS, F. S. The biological actions and therapeutic applications of the β -chloroethyl amines and sulfides. *Science*, 103: 409, 1946.
216. GOLUMBIC, C., FRUTON, J. S. and BERGMANN, M. Chemical reactions of the nitrogen mustard gases. i. The transformations of methyl-bis (β -chloroethyl) amine in water. *J. Organ. Chem.*, 11: 518, 1946.
217. GOLUMBIC, C. and BERGMANN, M. Chemical reactions of the nitrogen mustard gases. ii. The composition of aged unbuffered solutions of methyl-bis (β -chloroethyl) amine. *J. Organ. Chem.*, 11: 536, 1946.
218. FRUTON, J. S. and BERGMANN, M. Chemical reactions of the nitrogen mustard gases. iii. The transformations of the ethyl-bis (β -chloroethyl) amine in water. *J. Organ. Chem.*, 11: 543, 1946.
219. GOLUMBIC, C., STAHMANN, M. A. and BERGMANN, M. Chemical reactions of the nitrogen mustard gases. iv. The transformations of tris (β -chloroethyl) amine in water. *J. Organ. Chem.*, 11: 550, 1946.
220. FRUTON, J. S., STEIN, W. H. and BERGMANN, M. Chemical reactions of the nitrogen mustard gases. v. The reactions of the nitrogen mustard gases with protein constituents. *J. Organ. Chem.*, 11: 559, 1946.
221. FRUTON, J. S., STEIN, W. H., STAHMANN, M. A. and GOLUMBIC, C. Chemical reactions of the nitrogen mustard gases. vi. The reactions of the nitrogen mustard gases with chemical compounds of biological interest. *J. Organ. Chem.*, 11: 571, 1946.
222. GOLUMBIC, C., FRUTON, J. S. and BERGMANN, M. Chemical reactions of the nitrogen mustard gases. vii. Monosubstitution products of ethyl-bis (β -chloroethyl) amine and methyl-bis (β -chloroethyl) amine. *J. Organ. Chem.*, 11: 581, 1946.
223. STAHMANN, M. A. and BERGMANN, M. Chemical reactions of the nitrogen mustard gases. viii. The oxidation of the nitrogen mustard gases by peracids. *J. Organ. Chem.*, 11: 586, 1946.
224. STEIN, W. H., MOORE, S. and BERGMANN, M. Chemical reactions of mustard gas and related compounds. i. The transformations of mustard gas in water. Formation and properties of sulfonium salts derived from mustard gas. *J. Organ. Chem.*, 11: 664, 1946.
225. MOORE, S., STEIN, W. H. and FRUTON, J. S. Chemical reactions of mustard gas and related compounds. ii. The reaction of mustard gas with carboxyl groups and with the amino groups of amino acid and peptides. *J. Organ. Chem.*, 11: 675, 1946.
226. STEIN, W. H. and MOORE, S. Chemical reactions of mustard gas and related compounds. iii. The reactions of mustard gas with methionine. *J. Organ. Chem.*, 11: 681, 1946.
227. STEIN, W. H. and FRUTON, J. S. Chemical reactions of mustard gas and related compounds. iv. Chemical reactions of β -chloroethyl- β -hydroxyethylsulfide. *J. Organ. Chem.*, 11: 686, 1946.
228. STEIN, W. H., FRUTON, J. S. and BERGMANN, M. Chemical reactions of mustard gas and related compounds. v. The chemical reactions of 1, 2 bis (β -chloroethylthio) ethane. *J. Organ. Chem.*, 11: 692, 1946.
229. STAHMANN, M. A., FRUTON, J. S. and BERGMANN, M. Chemical reactions of mustard gas and related compounds. vi. The chemistry of sulfonium salts related to mustard gas. *J. Organ. Chem.*, 11: 704, 1946.
230. STAHMANN, M. A., GOLUMBIC, C., STEIN, W. H. and FRUTON, J. S. Chemical reactions of mustard gas and related compounds. vii. The chemistry of bis (β -chloroethyl) sulfone, divinyl sulfone and divinyl sulfoxide. *J. Organ. Chem.*, 11: 719, 1946.
231. GILMAN, A. Therapeutic applications of chemical warfare agents. *Federation Proc.*, 5: 285, 1946.
232. PHILIPS, F. S. and GILMAN, A. The relation between chemical constitution and biological action of the nitrogen mustards. P. 285. Approaches to Tumor Chemotherapy. American Association for the Advancement of Science, 1947.
233. HERRIOTT, R. M. Inactivation of viruses and cells by mustard gas. *J. Gen. Physiol.*, 32: 221, 1948.
234. HOUCK, C. R., CRAWFORD, B., BANNON, J. H. and SMITH, H. W. Studies on the mechanism of death in dogs of the systemic intoxication by the intravenous injection of methyl-bis (β -chloroethyl) amine or tris (β -chloroethyl) amine. *J. Pharmacol. & Exper. Therap.*, 90: 277, 1947.
235. GRAEF, I., KARNOFSKY, D. A., JAGER, V. B., KRICHESKY, B. and SMITH, H. W. The clinical and pathologic effects of the nitrogen and sulfur mustards in laboratory animals. *Am. J. Path.*, 24: 1, 1948.
236. KINDRED, J. E. Histologic changes occurring in the hemopoietic organs of albino rats after single injections of 2 chloroethyl vesicants; a quantitative study. *Arch. Path.*, 43: 253, 1947.
237. CAMERON, G. R., COURTICE, F. C. and JONES, R. P. The effects of β , β' -dichlorodiethyl methylamine hydrochloride on the blood-forming tissues. *J. Path. & Bact.*, 59: 425, 1947.
238. ANSLOW, W. P., JR., KARNOFSKY, D. A., JAGER, V. A. and SMITH, H. W. The toxicity and pharmacological action of the nitrogen mustards and certain related compounds. *J. Pharmacol. & Exper. Therap.*, 91: 224, 1947.
239. KARNOFSKY, D. A., GRAEF, I. and SMITH, H. W. Studies on the mechanism of action of the nitrogen and sulfur mustards *in vivo*. *Am. J. Path.*, 24: 275, 1948.
240. ROSE, H. M. and GELLHORN, A. Inactivation of influenza virus with sulfur and nitrogen mustards. *Proc. Soc. Exper. Biol. & Med.*, 65: 83, 1947.
241. SPURR, C. L. Influence of nitrogen mustards on the antibody response. *Proc. Soc. Exper. Biol. & Med.*, 64: 259, 1947.
242. CHEN, G. The effect of methyl-bis (β -chloroethyl) amine on *Trypanosoma equiperdum*. *J. Infect. Dis.*, 82: 133, 1948.
243. GILLETTE, R. and BODENSTEIN, D. Specific developmental inhibitions produced in amphibian em-

- bryos by a nitrogen mustard compound. *J. Exper. Zool.*, 103: 1, 1946.
244. BODENSTEIN, D. The effects of nitrogen mustard on embryonic amphibian development. I. Ectodermal effects. *J. Exper. Zool.*, 104: 311, 1947.
 245. FRIEDENWALD, J. S., BUSCHKE, W., SCHOLZ, R. O. and MOSES, S. J. Some effects of sulfur and nitrogen mustards on cell nuclei in mammalian cornea. P. 358. Approaches to Tumor Chemotherapy. American Association for the Advancement of Science, 1947.
 246. Staff of the Wilmer Institute. Studies on the physiology, biochemistry, and cytopathology of the cornea in relation to injury by mustard gas and allied toxic agents. *Bull. Johns Hopkins Hosp.*, 82: 81, 1948.
 247. AUERBACH, C. and ROBSON, J. M. Chemical production of mutations. *Nature, London*, 157: 302, 1946.
 248. AUERBACH, C., ROBSON, J. M. and CARR, J. G. The chemical production of mutations. *Science*, 105: 243, 1947.
 249. STAHMANN, M. A. and STAUFFER, J. F. Induction of mutants in *Penicillium notatum* by methyl-bis (β -chloroethyl) amine. *Science*, 106: 35, 1947.
 250. HOROWITZ, N. H., HOULAHAN, M. B., HUNGATE, M. G. and WRIGHT, B. Mustard gas mutations in *Neurospora*. *Science*, 104: 233, 1946.
 251. BODENSTEIN, D. and KONDRITZER, A. A. The effect of nitrogen mustard on nucleic acids during embryonic amphibian development. *J. Exper. Zool.*, 107: 109, 1948.
 252. BOYLAND, E. The pharmacology of chloroethylamines. *Biochem. Soc. Symposium*, 2: 61, 1948.
 253. GOODMAN, L. S., WINTROBE, M. M., DAMESHEK, W., GOODMAN, M. J., GILMAN, A. and MCLENNAN, M. T. Nitrogen mustard therapy. Use of methyl bis (β -chloroethyl) amine hydrochloride and tris (β -chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. *J. A. M. A.*, 132: 126, 1946.
 254. BURCHENAL, J. H. The newer nitrogen mustards in the treatment of leukemia. *Radiology*, 50: 494, 1948.
 255. WINTROBE, M. M., HUGULEY, C. M., JR., MCLENNAN, M. T. and DE CARVALHO LIMA, L. P. Nitrogen mustard as a therapeutic agent for Hodgkin's disease, lymphosarcoma and leukemia. *Ann. Int. Med.*, 27: 529, 1947.
 256. APTHOMAS, M. I. R. and CULLUMBINE, H. Nitrogen mustards in Hodgkin's disease, report on 21 cases and 4 other reticuloses. *Lancet*, 1: 899, 1947.
 257. OSBORNE, E. D., JORDON, J. W., HOAK, F. C. and PSCHIERER, F. J. Nitrogen mustard therapy in cutaneous blastomatous disease. *J. A. M. A.*, 135: 1123, 1947.
 258. KARNOFSKY, D. A., CRAVER, L. F., RHOADS, C. P. and ABELS, J. C. An evaluation of methyl bis (β -chloroethyl) amine hydrochloride and tris (β -chloroethyl) amine hydrochloride (nitrogen mustards) in the treatment of lymphomas, leukemias and allied disorders. Approaches to tumor chemotherapy. P. 319. American Association for the Advancement of Science, 1947.
 259. JACOBSON, L. O., SPURR, C. L., BARRON, E. S. G., SMITH, T., LUSBAUGH, C. and DICK, G. F. Nitrogen mustard therapy—studies on the effect of methyl bis (β -chloroethyl) amine hydrochloride on neoplastic diseases and allied disorders of the hemopoietic system. *J. A. M. A.*, 132: 263, 1946.
 260. SPURR, C. L., JACOBSON, L. O., SMITH, T. R. and BARRON, E. S. G. The clinical application of methyl bis (β -chloroethyl) amine hydrochloride to the treatment of lymphomas and allied dyscrasias. Approaches to Tumor Chemotherapy. P. 306. American Association for the Advancement of Science, 1947.
 261. KARNOFSKY, D. A. The nitrogen mustards and their application in neoplastic disease. *New York State J. Med.*, 47: 992, 1947.
 262. RHOADS, C. P. Nitrogen mustards in the treatment of neoplastic disease. Official statement. *J. A. M. A.*, 131: 656, 1946.
 263. WINTROBE, M. M., MCLENNAN, M. T., HUGULEY, C. M., JR. Clinical experiences with nitrogen mustard therapy. Approaches to Tumor Chemotherapy. P. 347. American Association for the Advancement of Science, 1947.
 264. WILKINSON, J. F. and FLETCHER, F. Effect of β -chloroethyl amine hydrochloride in leukemia. Hodgkin's disease, and polycythemia vera. Report of 18 cases. *Lancet*, 2: 540, 1947.
 265. BORTZ, D. W. and HADEN, R. L. Nitrogen mustard therapy. Report of 16 cases thus treated. *Cleveland Clin. Quart.*, 14: 218, 1947.
 266. HENSTELL, H. H., TOBER, J. N. and NEWMAN, B. A. The influence of nitrogen mustards on mycosis fungoides. Observations relating its effect to the reticulo-endothelial system. *Blood*, 2: 564, 1947.
 267. SNIDER, G. E. Treatment of Boeck's sarcoid with nitrogen mustard. A preliminary report. *South. M. J.*, 41: 11, 1948.
 268. COWDRY, E. V. The Fourth International Cancer Research Congress. St. Louis, September 2-7, 1947. *J. A. M. A.*, 135: 1067, 1947.
 269. PHILPOTT, O. S., WOODBURN, A. R. and WALDRIF, G. A. Nitrogen mustard in the treatment of mycosis fungoides. *J. A. M. A.*, 135: 631, 1947.
 270. HETTIG, R. A. Result of methyl bis (β -chloroethyl) amine hydrochloride therapy. A preliminary report of a nitrogen mustard. *J. Lab. & Clin. Med.*, 32: 1431, 1947.
 271. RHOADS, C. P. Recent advances in treatment of cancer. *J. A. M. A.*, 136: 305, 1948.
 272. TAFEL, M. Experiences in treatment of neoplastic disease with nitrogen mustard. *Yale J. Biol. & Med.*, 19: 441, 1947.
 273. HOFMEYER, H. O. Clinical experiences with nitrogen mustards in Hodgkin's disease. *South African M. J.*, 21: 195, 1947.
 274. SHERRY, M. Nitrogen mustards in the treatment of Hodgkin's disease and lymphosarcoma. *South. M. J.*, 41: 118, 1948.
 275. FALLOON, W. W. and GORHAM, L. W. Clinical experience with nitrogen mustard. *New York State J. Med.*, 48: 612, 1948.
 276. CRAVER, L. F. The nitrogen mustards: clinical use. *Radiology*, 50: 486, 1948.

277. CRAVER, L. F. Lymphomas and leukemias. *Bull. New York Acad. Med.*, 23: 79, 1948.
278. SPURR, C. L., SMITH, T. R. and JACOBSON, L. O. Chemotherapy in human lymphomas, leukemias, and allied disorders of the hemopoietic system. *Radiology*, 50: 387, 1948.
279. JACOBSON, L. O., SPURR, C. L., SMITH, T. R. and DICK, G. J. Radioactive phosphorus and alkylamines in the treatment of neoplastic and allied diseases of the hemopoietic system. *M. Clin. North America*, 31: 3, 1947.
280. ALPERT, L. K. and PETERSON, S. S. The use of nitrogen mustard in the treatment of lymphomata. *Bull. U. S. Army M. Dept.*, 7: 187, 1947.
281. WINTROBE, M. M. and HUGULEY, C. M. Nitrogen mustard therapy for Hodgkin's disease. *Cancer*, 1: 357, 1948.
282. SMITH, T. R., JACOBSON, L. O., SPURR, C. L., ALLEN, J. G. and BLOCK, M. H. A coagulation defect produced by nitrogen mustard. *Science*, 107: 474, 1948.
283. BOYLAND, E., CLEGG, J. W., KOLLER, P. C., RHODEN, E. and WARWICK, O. H. The effects of chloroethylamines on tumors, with special reference to bronchogenic carcinoma. *Brit. J. Cancer*, 2: 17, 1948.
284. KARNOFSKY, D. A. Personal communication.
285. KIERLAND, B. R., WATKINS, C. H., and SCHULLENBERGER, C. C. The use of nitrogen mustard in the treatment of mycosis fungoides. *J. Invest. Dermat.*, 9: 195, 1947.
286. KARNOFSKY, D. A. Chemotherapy of neoplastic disease. *New England J. Med.*, 239: 226, 260, 299, 1948.

Seminars on Congestive Failure

The Role of the Cardiac Output in the Mechanisms of Congestive Heart Failure*

EUGENE A. STEAD, JR., M.D.

Durham, North Carolina

SYMPTOMS of heart disease are of two types: (1) those caused by failure of the heart as a pump and (2) those caused by local ischemia of heart muscle. It is common clinical knowledge that the patient may have angina pectoris without congestive failure or congestive failure without angina. In the first instance the heart responds normally to exercise with an increase in cardiac output. A local area of the heart muscle increases its metabolism without being able to increase its blood supply proportionately because of coronary artery disease. Substances which accumulate in working muscles poorly supplied with blood stimulate sensory nerve endings and the subject is conscious of substernal pain. The heart pumps the required amount of blood for the needs of the body and pain stops further exertion. In the second instance, the heart does not perform its work well as a pump. Symptoms from this cause limit exertion before an area of local ischemia occurs. The picture is that of congestive heart failure rather than angina pectoris.

Congestive heart failure differs from the circulatory failure commonly produced by various means in the laboratory in that the arterial pressure is well maintained and that the condition lasts for days, weeks and years. The symptoms of congestive failure can be divided into two groups: (1) those resulting from the inability of the heart to increase its output normally in response to increased peripheral need for blood. The muscular weakness of congestive failure is a familiar example. (2) Those resulting

from congestion and edema of the lungs, liver, skin and other organs. There has been no controversy about the first group of symptoms. There has been little agreement about the chain of events leading to congestion and edema.

It has seemed logical to relate the congestion and edema of the various organs to the failure of the heart as a pump. Accordingly, the cardiac output has been investigated in normal subjects and in those with congestive heart failure. The methods in which a foreign gas has been used have been largely replaced today by the method of right heart catheterization utilizing the Fick principle. This technical advance has allowed the study of patients who were too ill to cooperate actively in the breathing maneuvers required by the foreign gas methods.

As measured by the technic of right heart catheterization, the cardiac output in normal subjects under basal conditions is around 3.3 L. per minute per sq. M. of body surface.¹ The spread of values for normal, relaxed, fasting subjects is considerable, ranging from 2.3 to 4.1 L. The output is increased by apprehension, exercise, sudden lowering of peripheral resistance, intake of food and administration of epinephrine. The mechanisms for increasing the cardiac output are complex and have not been clearly defined in man.² Changes in right atrial pressure do not cause the consistent changes in cardiac output which are seen in the heart-lung preparation. The increased cardiac output of

* From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

anemia, thyrotoxicosis, apprehension and sudden lowering of peripheral resistance are not accompanied by increase in right atrial pressure.

The cardiac output is decreased by motionless standing, by large hemorrhage and by myxedema. Lowering of the mean right atrial pressure by 3 to 4 cm. of water, by venesection or by pooling of blood in the extremities does not cause a consistent fall in cardiac output.³

As measured by the Fick principle, the cardiac output is determined by two factors: (1) the arterial-mixed venous oxygen difference and (2) the oxygen consumption per minute. A rise in metabolism without an increase in A-V oxygen difference or a decrease in A-V difference without a fall in metabolism both indicate a rise in cardiac output. In apprehension the decrease in A-V oxygen difference and a less marked rise in oxygen consumption give a high output.¹ In light exercise a rise in oxygen consumption and a slight increase in A-V oxygen difference indicate a high output.⁴

In congestive heart failure the resting cardiac output, as measured by the foreign gas methods and by the direct Fick principle, is usually decreased.⁵ This decrease is more striking if considered in relation to the two measurements from which the cardiac output is derived. Fewer liters of blood per minute are pumped by the heart and more oxygen is removed from each liters by the tissues to compensate for slow blood flow. For any given level of anxiety or work the patient with *uncomplicated* congestive failure has an A-V oxygen difference greater than normal.^{4,5} The stimulus of exercise may raise the cardiac output somewhat above the resting level. That the response is abnormal is shown by the fact that at any level of oxygen consumption the A-V oxygen difference is wider than in a normal subject with an equal oxygen consumption. In spite of the fact that the majority of patients with congestive heart failure show these findings, there are some who show a normal cardiac output and in a few the output is elevated. Because of these excep-

tions the question arises: Is a reduction in cardiac output an essential part of the picture of congestive failure?

Patients with thyrotoxicosis, anemia and arteriovenous fistula have abnormally high values for the resting cardiac output.² It is not surprising that when the heart fails in the presence of these complicating factors, the signs of congestive failure are present before the circulation falls below that found in a resting normal subject of the same size. The output, although high in the terms of the normal, is insufficient for the demands created by the physiologic or pathologic circumstances; and signs of circulatory insufficiency develop even though the output is still considerable.

Probably too much emphasis has been placed on the development of congestive failure with an output above the resting level. This actually seems to be the rule rather than the exception in the first bout of congestive failure which comes on slowly. The patient notices fatigue, dyspnea and a low urine output during the day. At night he is awakened several times to void and notes that the night urine is increased in amount. At this stage of failure the cardiac output is found to be normal at rest. During his daily activity when the signs of congestion are developing, the cardiac output is increased above the level of rest but not to the degree required by the activity; and the signs of congestion develop in spite of an output above the resting level. The fact that the output although high is not as high as is needed is shown by the wide A-V oxygen difference.

According to this interpretation, the congestive phenomena of heart failure occur whenever over a long period of time the cardiac output is insufficient to supply the organs and tissues of the body with the optimal amount of blood. The optimal amount of blood will vary with activity and disease. In thyrotoxicosis in failure the output will be high because of the increased oxygen consumption; in beriberi it will be high because of the peripheral vasodilatation caused by the metabolic defect. In

either instance congestive failure will develop whenever organ blood flow falls below the level required by the altered metabolism. In heart failure the blood flow to all organs is probably slightly below the optimal level, but that through the kidney is particularly decreased. The fall in renal blood flow eventually reaches the point where the glomerular filtrate is reduced and abnormal retention of sodium occurs.

The massive edema so characteristic of congestive failure occurs only when sodium chloride and water are retained by the kidneys. This does not mean that pulmonary edema cannot occur except by the renal mechanism. It does mean that edema associated with gain of weight requires a renal mechanism. In the sudden pulmonary edema caused by a massive myocardial infarct of the left ventricle there is no time for sodium retention. The blood is forced into the lungs by the right heart and cannot be removed by the left. Rapid and frequently fatal pulmonary edema may develop. A consideration of this problem brings up the question of failure of the right or left ventricles as contrasted to failure of both chambers of the heart.

The available data favor the view that two factors are important in the pulmonary congestion of congestive failure: (1) left ventricular failure; (2) retention of sodium and water by the kidneys.

Clinical observation teaches us that the lungs are involved early in heart failure caused by hypertension, luetic aortitis and coronary artery disease. The lungs contain too much blood and water, as shown by dyspnea, decreased vital capacity, increased circulation time and high pulmonary arterial pressure. These symptoms of pulmonary congestion usually precede the onset of generalized pitting edema and the rise in systemic venous pressure. The physiologic and pathologic evidence would favor the view that the lungs are engorged because at times the right ventricle pumps blood into the lungs at a faster rate than the left ventricle pumps it out. This increases the pulmonary capillary pressure and causes a large

amount of fluid retained by the kidney to localize in the lungs. Where does this blood come from which the right ventricle pumps into the lungs? It is the blood pumped to it by the left ventricle plus the amount of blood that the right ventricle receives from the systemic circulation by a combination of two mechanisms: (1) Recent work has demonstrated that the right side of the heart can increase its output in the face of a moderate fall in right atrial pressure.² Thus, when appropriately stimulated the right side of the heart may deliver blood into the lungs without a corresponding increase in output of the left ventricle by allowing the right atrial pressure to fall. (2) Active constriction of the systemic venous bed can deliver to the right side of the heart a quantity of blood which is not dependent on the output of the left ventricle. Thus, physiologic, pathologic and clinical data support the concept that backing up of blood behind a failing left ventricle is a common occurrence in the usual types of heart disease.

The concept of right ventricular failure developing later in the course of heart disease with backing up of blood behind the right side of the heart because of right ventricular failure is much harder to visualize. Clinical observation shows that as heart failure advances peripheral edema and a rise in systemic venous pressure occur. Consider the quantitative aspects of the problem. The blood available for backing up behind the right side of the heart is that pumped out by the left ventricle plus that normally available in the systemic venous bed. The blood pumped out by the left ventricle is that delivered to it by the right side of the heart plus that which might be delivered to the left ventricle by active pulmonary venous constriction. It is doubtful if the lungs can deliver enough blood to the left side of the heart to flood the peripheral circulation. Further doubt is thrown on the thesis of right ventricular failure because of the clinical evidence that left ventricular failure continues to persist as the dominant lesion even after edema and

increased peripheral venous pressure occur. If such a person is made free of peripheral edema by sodium restriction in the diet, the abnormalities in the pulmonary circulation will persist although there is no detectable edema and the right atrial pressure is normal.

It would appear that in the usual patient with heart failure the concept of flooding of the lungs from left ventricular failure is a sound explanation for the pulmonary congestion, but that the available evidence is against the flooding of the systemic circulation by right ventricular failure as a cause of the increased venous pressure and systemic edema.

The picture of left ventricular failure uncomplicated by sodium retention is seen most commonly in patients with massive infarction of the left ventricle. Blood enters the lung from the right ventricle; the damaged left ventricle must let it remain there. Massive pulmonary edema develops rapidly without an increase in body weight. In the more common types of left ventricular failure the picture does not seem quite as simple. Although pitting edema is absent, the patient has usually retained a few pounds of fluid. Furthermore, the administration of a mercurial diuretic frequently lessens the edema without any detectable improvement in left ventricular function. Conversely, a high salt intake makes the dyspnea worse. These clinical considerations point to the conclusion that while a rise in pulmonary capillary pressure alone may cause pulmonary edema, this rise in pulmonary capillary pressure is commonly accompanied by retention of salt and water by the body, and that these two factors together are responsible for the dyspnea and orthopnea of left ventricular failure.

We now return to the original question: Is the disproportion between the output of the two ventricles responsible for the picture of congestive failure without regard to the absolute level of the cardiac output? The answer is both yes and no. The lungs can be flooded from the systemic circulation

and this can conceivably occur with a level of output of the left ventricle adequate to supply satisfactorily all the needs of the body for blood. In most instances, the picture of backing up of blood behind the left ventricle appears to be accompanied by a simultaneous retention of salt and water. The flooding of the systemic circulation by the lungs seems unlikely, and the increased systemic venous pressure and peripheral edema in the usual patient with heart failure cannot be explained by backing up of blood behind a failing right ventricle.

The increase in systemic venous pressure in patients with heart failure has frequently been interpreted as a compensatory mechanism for maintaining the output of a failing heart. Clinical evidence to support this interpretation has never been very convincing. The situation differs from the heart-lung preparation in that marked chronic dilatation of the heart chambers and hypertrophy of the muscle have occurred. A dilated right heart apparently fills completely over a wide range of venous pressures. Although direct observations are lacking, it seems likely that the same is true for the left ventricle. The primary defect seems to be in ventricular emptying. Systole leaves a large quantity of residual blood in the heart. During diastole the ventricle fills to full capacity and wide variations in right atrial pressure have little effect on output. In patients with chronic fixed failure the venous pressure varies with the sodium intake.⁶ Studies on these subjects show no beneficial effects of a high right atrial pressure.

It is certainly true that the heart of a patient with failure does not always respond to a given stimulus in the same way as it does in a normal subject. Exercise in the normal subject causes the output to rise. In certain patients with congestive failure the output may fall with exercise.⁴ In normal subjects apprehension causes a rise in cardiac output; in the cardiac it may cause a fall. In the normal subject venesection causes no consistent change in out-

put;³ in the patient with pulmonary edema from heart failure venesection causes a rise in cardiac output.^{7,8} In these examples one sees that the failing heart, when pushed too far, becomes even sicker and the output falls. The author believes that the increased load on the circulation may cause a further decrease in the ability of the heart to empty. Lessening of the load by sedation or rest or relieving the intense reflex activity of pulmonary edema by venesection, tourniquets or mercurial diuretics may increase the ability of the heart to empty. According to this conception the progressive failure of the heart occurs from fatigue, and overdistention of the ventricular muscles by a high venous pressure is not a fundamental part of the failure. Conventional physiology attributes the further failure of the heart with exercise or pulmonary edema to a rise in venous pressure and overdistention of the heart. Time will determine which interpretation is correct.

The heart in failure responds to digitalis by an increase in output. This is accomplished by a more complete emptying of the heart in systole. The increase in output may be accompanied by a striking or insignificant fall in right atrial pressure. In certain borderline patients in whom the cardiac output is at the lower limit of normal, a significant rise with digitalis demonstrates that the output is not optimal for that particular patient.

SUMMARY

If one measures the cardiac output at rest in patients with failure, the following combinations will be found:

1. Cardiac output low with failure remains low when symptoms are relieved by sodium restriction or continued use of diuretics. These are the usual findings in fixed intractable heart failure.

2. Cardiac output low with failure in-

creases with administration of digitalis or when such complications as pulmonary infarction clear up. This condition does not require salt restriction or diuretics when activity is reduced by bed rest.

3. Cardiac output normal with failure remains normal on compensation. Decomensation develops with increased activity. Cardiac output adequate for diuresis at rest; symptoms at time of study because of waterlogging of body which persists until diuresis is completed.

4. Cardiac output high with failure falls when the stimulus for an increased output is removed. This combination may be shown (1) by restless, apprehensive, dyspneic patients whose output is adequate for rest but inadequate for mild exertion; and (2) by patients with hyperthyroidism, anemia, arteriovenous fistula, patent ductus arteriosus, beriberi and certain infections.

REFERENCES

1. STEAD, E. A., JR., WARREN, J. V., MERRILL, A. J. and BRANNON, E. S. The cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting. *J. Clin. Investigation*, 24: 326-331, 1945.
2. STEAD, E. A., JR. and WARREN, J. V. Cardiac output in man. An analysis of the mechanisms varying the cardiac output based on recent clinical studies. *Arch. Int. Med.*, 80: 237-248, 1947.
3. WARREN, J. V., BRANNON, E. S., STEAD, E. A., JR. and MERRILL, A. J. The effect of venesection and the pooling of blood in the extremities on the atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances. *J. Clin. Investigation*, 24: 337-344, 1945.
4. HICKAM, J. B. and CARGILL, W. H. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J. Clin. Investigation*, 27: 10-23, 1948.
5. STEAD, E. A., JR., WARREN, J. V. and BRANNON, E. S. Cardiac output in congestive heart failure. *Am. Heart J.*, 35: 529-541, 1948.
6. WARREN, J. V. and STEAD, E. A., JR. Fluid dynamics in chronic congestive heart failure. *Arch. Int. Med.*, 73: 138-147, 1944.
7. McMICHAEL, JOHN. Personal communication.
8. Unpublished observations from this laboratory.

Conference on Therapy

Household Poisonings

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. HARRY GOLD: The conference today is on the subject of household poisons. It is not very easy to draw a line around the group of household poisons as it seems to include many of the poisons used in industry, many of the medicines found in drug stores and chemicals found in the grocery stores, paint stores and others. I suppose that the best we can do is to consider a few of the more common poisons and perhaps some of the more interesting.

Any one physician may not see a great many cases of poisoning in the home, but in the aggregate the number of cases is very large. In one report, made in 1934 by Aikman of Rochester, attention was called to the fact that 1 per cent of all the children in the Strong Memorial Hospital were admitted for some form of poisoning. About one-quarter of all those cases were accidental poisonings and about one-half were therapeutic poisonings. That one of every one hundred children in a hospital was there because of poisoning indicates that the topic of the conference today is one of major importance. Perhaps in the course of the discussion we may learn how these matters stand in the New York Hospital.

The major proportion of household poisonings occur in children. There is a report to the effect that in 1929 in the United States there were 530 deaths due to accidental poisoning in children under five. The numbers declined all the way down to fifty cases during the next five-year age period. It seems that in the age group up to five there is a population of individuals who go rummaging about, picking up medicines

and swallowing things they have no business to be swallowing. The drugs and chemicals involved in these poisonings cover a very wide field. In one report listing 158 cases of fatal poisonings in a five-year period in children under five years of age in New York State there were forty-five different substances listed. One poison stood out in that group. Would anybody venture a guess?

STUDENT: Camphor?

DR. GOLD: No.

STUDENT: Rat poison?

DR. GOLD: No.

STUDENT: Lead?

DR. GOLD: No.

STUDENT: Phosphorus?

DR. GOLD: No.

DR. JANET TRAVELL: Phenolax?

DR. GOLD: No.

STUDENT: Aspirin?

DR. GOLD: No.

STUDENT: Alcohol?

DR. GOLD: No. You must remember these were all individuals under five years of age.

STUDENT: How about iodine?

DR. GOLD: No.

DR. TRAVELL: Strychnine?

DR. GOLD: That is correct. About one-half of all the cases of fatal poisonings in this group, namely, 75 of the 158, were due to strychnine. There was no close second in the entire list. The remaining eighty-three cases were caused by forty-four different substances. The cases of strychnine poisoning were due to the use of cathartic and "tonic" pills. The cathartic pills, containing

aloin, strychnine and belladonna, the so-called A. S. et B. pills, and those containing in addition resin of podophyllum and extract of cascara, or the so-called Hinkle's pills, were the chief offenders. Incidentally, the more recent edition of the National Formulary (1946) has eliminated strychnine from the Hinkle's pills but has doubled the dose of strychnine in the A. S. et B. pill, from $\frac{1}{120}$ to $\frac{1}{60}$ gr. These are very tiny pills and if a child about five years of age helps himself to about ten or fifteen of these innocent looking pellets, he develops severe strychnine poisoning and may die with convulsions.

We receive fairly frequent inquiries in relation to cases of poisoning. It is usually a telephone call for suggestions. I am in the habit of making a memo of the circumstances and placing it in a folder. It might be interesting to have a look at a few of these at random. This may give us some idea of the nature of the problem in a case of household poisoning.

Here is a case of atropine poisoning. The record is dated 1935 but there have been additional similar ones since. Someone in the family received atropine drops for use in the eyes. The two year old baby helped itself to the bottle and, according to the account, swallowed the contents, about 20 cc. of a 1 per cent solution of atropine sulfate. The doctor arrived an hour and one-half later and found the baby hot, flushed, restless, conscious, with dilated pupils and a fever of 102°F. He promptly washed the stomach and brought the patient to the hospital. In the next few hours, because the condition of the patient seemed unchanged, treatment was instituted. The baby received a dose of 10 mg. per Kg. of amytal sodium intramuscularly. From that point on the real trouble began. The patient quite promptly went into a very deep stupor and then coma, with very shallow respiration. The pulse became feeble and cyanosis developed. The Drinker respirator was installed for any possible emergency. Nothing happened. The following day the child woke up and seemed to

be well on the way to recovery. Here is a case which started out as a possible accidental poisoning by atropine but ended up as a therapeutic poisoning with amytal sodium. The baby received the equivalent of about 12 gr. (0.8 Gm.) of amytal, normally given an adult. Such a dose is not likely to prove fatal but produces a fairly high degree of depression in a great many people. The dose of atropine presents a point of interest. It is commonly stated that the fatal dose of atropine for children is about 10 mg. and for adults about 100 mg. I am not aware of any proof of deaths in either children or adults from such doses. There is a statement in the literature to the effect that the smallest recorded dose which proved fatal was 95 mg. in a child and 130 mg. in an adult. On this basis the patient took about twenty times the fatal dose of atropine. I believe that the dose of atropine stated in the literature to be fatal is much too small. From experience in animals atropine produces pronounced symptoms after very small doses due to blocking of the autonomic nervous system, but these actions are not the ones which cause the fatality and the fatal effects require massive doses. In a cat, for example, a small fraction of a mg. per Kg. blocks the cardiac vagus, but the fatal dose is of the order of 50 mg. per Kg. Humans may be much more sensitive to the fatal action of atropine, but indications from the isolated reports of atropine poisoning are that in humans also a wide gap exists between the dose which causes very disturbing symptoms and the one which causes death. For example, a 10 mg. dose of atropine is apt to produce delirium but recovery is reported from a dose as high as 500 mg. In the case in question there also remains the possibility that the child might not have swallowed all the solution that disappeared from the bottle for a 1 per cent solution of atropine is fairly bitter.

I cite this case merely as an illustration of a fact which I think applies to household poisonings in general, namely, the danger of treatment. When one does not know what is best to do, it is probably best to do nothing.

ing. In the reported cases of poisoning with atropine, maniacal delirium frequently occurs and that has been controlled by a barbiturate. In the case to which I have just referred, however, there was no delirium and, therefore, no indication for use of a large dose of amytal.

Here is the record of another inquiry. A baby was having its temperature taken by rectum. The thermometer broke and the mercury remained in the rectum. What should be done? What is the chance of serious poisoning from mercury? I have two additional inquiries of a similar nature, but in these the children bit off the bulb of the thermometer and swallowed the mercury. All of these queries were answered in the same way: Let them be and do nothing about it. The average clinical thermometer contains about 1 Gm. of mercury. There was a time when as much as 100 to 500 Gm. of metallic mercury was given orally for the treatment of ileus. In rare cases this dose caused death. There is no doubt of the fact that some absorption takes place from metallic mercury given in bulk but the amount absorbed from a dose given in that way must be very small. There is the account of a man who attempted suicide by injecting 2 cc. or 27 Gm. of metallic mercury into his vein; he developed some diarrhea but lived about ten years. It is otherwise when the metallic mercury is finely divided. It used to be a fairly common practice to give children as much as 100 mg. of metallic mercury in the form of a dose of 0.25 Gm. of mercury with chalk in a capsule for the treatment of syphilis. These experiences suggest that the mercury released from the broken bulb of the thermometer may be ignored with impunity. This was done in the three cases to which I have referred and there were no reasons to regret it.

I have a memorandum on a telephone call from a pediatrician regarding the possibility of poisoning from matches. The child was playing with a box of safety matches and chewed off the tips. Precisely how many had been chewed he did not know

but he was informed that it was the contents of a nearly full small box. The problem related to the possibility of phosphorus poisoning. He was reassured to learn that to get into difficulties from that adventure the child would have had to consume the box rather than the matches.

The friction match which can be struck anywhere was originally tipped with yellow phosphorus and fifteen or twenty tips might provide a fatal dose of phosphorus. But in the safety match the phosphorus is on the striking surface of the box and even this in present day matches no longer contains the highly toxic, yellow phosphorus but the unabsorbable red phosphorus. The latter is relatively non-toxic although some contamination with yellow phosphorus is a source of danger. Incidentally, even the ordinary match, which may be struck anywhere, is now relatively innocuous because the non-toxic phosphorus sesquisulfide has replaced the yellow phosphorus.

There is here an inquiry regarding a barbiturate. A baby, seven months old, got his hands on a capsule of 0.2 Gm. of amytal sodium and swallowed it about thirty minutes previously. There are, at this time, no appreciable effects. What should be done? The suggestion was made to empty the stomach or wash it. This was not imperative. It would only result in eliminating the protracted period of stupor or shortening the period of deep sleep. Since the total dose represented only about 30 mg. per Kg., the risk of fatal barbiturate poisoning was negligible. Considerably larger doses used to be extensively employed to induce anesthesia for surgical operations. This is a good example of poisoning in which, as is very often the case, the patient does well without treatment.

We recently had an inquiry about moth balls in connection with a child who had eaten some. Many materials may be involved in poisoning by moth balls or other moth repellent articles, namely, camphor, naphthalene and paradichlorobenzene. Paradichlorobenzene is the compound now most widely used in the various forms of

moth repellent materials. Exposure to its fumes over long periods of time causes poisoning, but by oral administration the compound is relatively innocuous. In the dog feeding of 1.0 Gm. per Kg. daily (equivalent to about 60 Gm. for an average adult) for a long period of time has been found to produce no toxic effects. This compound appears in the home in such forms as nuggets, flakes, cakes and pellets. The smaller nuggets weigh about 0.25 Gm. and the larger ones as much as 7 Gm. Should an infant or a very young child consume three or four of the larger nuggets, it is unlikely that serious poisoning would occur. Some moth repellent materials contain naphthalene or a mixture of naphthalene and paradichlorobenzene. We recently examined a trade box of moth balls which contained only naphthalene, each ball weighing approximately 2.5 Gm. Naphthalene is more toxic than paradichlorobenzene. It is used in doses of 0.5 Gm. in the treatment of oxyuris infestations. Death has been reported in a child from as little as 2 Gm., but the fatal dose of naphthalene for most cases is considerably larger. It seems unlikely that the consumption of a naphthalene moth balls by an infant or young child would prove serious. The few recorded cases of naphthalene poisoning refer to such symptoms as abdominal cramps, nausea and vomiting, motor instability and irritation of the urinary tract with burning in the urethra and urgency. It is apparently also damaging to the liver and kidney, giving rise to jaundice and albuminuria. The cases of poisoning by paradichlorobenzene in individuals exposed to the fumes for long periods of time are characterized by injury to the liver and by cataracts.

Camphor is now rarely found in moth balls although these are sometimes referred to as camphor balls. Camphor cakes are still available and used as moth repellents. It is the experience that camphor taken by mouth may cause dramatic and threatening symptoms but most patients recover. We shall refer to camphor again presently.

A word about the general problem of moth repellent articles is in order at this point. A doctor recently telephoned me about a child that had taken a quantity of a moth repellent known as Expello. We examined several brands of moth repellent nuggets with the label stating clearly that these represented paradichlorobenzene. However, the can of Expello gave no indication of the nature of the contents. The pellets in this can had a somewhat different smell from those labeled paradichlorobenzene. That threw us off the track although we were aware of the fact that the most common moth repellents are chiefly paradichlorobenzene. The manufacturer of Expello is in New Hampshire and was, therefore, not readily accessible to us, but a label was inscribed on the can stating that it was guaranteed by the Good Housekeeping Institute. We, therefore, contacted them for information about this material. They gave us the information, namely, that Expello represents paradichlorobenzene. There is something wrong about having such a material which is always so accessible to children in the household without the name of the chemical clearly stated on the container. It is hardly to be expected that the physician will be familiar with the chemical composition of all moth repellent articles under proprietary names which give no indication of the nature of the product. It would have spared the family a good deal of anguish and the physician no end of trouble if the name paradichlorobenzene had appeared somewhere on the label for even if this compound might not have caused any harm by reason of its low toxicity, the physician would be forced to take measures in treatment which would have been unnecessary had the name of the compound been known to him. Another disturbing aspect of this experience was the fact that of the three cans in our possession the only one which failed to disclose the contents was the one bearing the seal of the Good Housekeeping Institute. I presume that housewives take the seal of the Good Housekeeping Institute seriously and are likely

to prefer articles bearing its name. Under the circumstances I wonder whether the Good Housekeeping Institute ought not to recognize a moral obligation in the matter and insist on the chemical name appearing on the container of articles which may, rightly or wrongly, find their way into the mouth of a youngster rummaging about in the house. A person in charge of these matters in the Institute informed me that the label was entirely adequate within the meaning of the law and that this moth repellent, Expello, did not fall in the class of so-called "economic poisons." We should take cognizance of the fact that a substance which is not classed as a so-called economic poison is not necessarily non-toxic. The criteria for an economic poison merely differentiate between those articles which take small doses to kill and those which require somewhat larger doses to kill. For example, in an extreme case, if the average lethal dose per Kg. were 49 mg., it would be classed as an economic poison, whereas if the average lethal dose were 51 mg., the article would stand outside of the class of economic poisons. I think this is not an improper place to suggest that something be done to insure that when a doctor is called upon to treat a possible case of poisoning by a common household material, the label on the container inform him of the exact nature of the chemical and the amount of it that is present in the preparation. Without that information, he is often quite helpless.

Camphorated oil is sometimes mistaken for castor oil and it might be well therefore to know something about the toxicity of camphorated oil. Camphor is a convulsant but it is very rapidly eliminated so that even after a fairly violent convulsion the individual is likely to recover. While there are a great many cases of camphorated oil poisonings, the number of deaths is very low even in cases in which violent convulsions have occurred. Camphorated oil is a 20 per cent solution of camphor in oil, and the smallest oral doses of camphor which are on record as causing death are of the order of 1.5 Gm.

That would make about two teaspoonfuls of camphorated oil. There have been instances of mass poisoning from camphorated oil. In one series each of some twenty children received from 1 to 1.5 tablespoonfuls of camphorated oil. Most of them developed convulsions but they all recovered.

Infants and children seem to have little trouble in getting hold of a bottle or can of kerosene or gasoline. Also they do not seem to have any particular aversion to drinking it. There are still places in the country in which kerosene is used in doses of a few cc. for the treatment of bronchitis and colds. A considerable number of cases of poisoning are encountered. There are recoveries from as much as 125 cc. of kerosene and deaths from as little as 30 cc. There is the case of an adult who recovered from 750 cc. There is not enough information to be certain whether kerosene or non-leaded gasoline is more toxic. The course of kerosene poisoning is very rapid. Effects appear within a few minutes with gastrointestinal symptoms (vomiting, diarrhea, abdominal cramps) and central nervous system symptoms (coma, convulsions). About 5 to 10 per cent of the patients die and this takes place in less than twenty-four hours. The remainder seem to recover completely and fairly promptly. It is fairly safe to assume that the patient who is still alive on the day after a dose of kerosene is likely to recover. It behaves in many respects like a volatile anesthetic. The lungs seem to be involved in a large proportion of the cases and such a case may be mistaken for one of primary pneumonia. It is not certain how the lungs become involved, whether by excretion of the volatile agent through the lungs or aspiration during vomiting. It is noteworthy that in animal experiments the fatal dose by stomach is about ten times that by intratracheal injection. This may indicate rapid absorption from the pulmonary bed or marked inflammatory reaction to the high concentration. It is obvious that the stomach should be washed if the time interval suggests that any appreciable amount may still be there and special care needs to be taken

to avoid aspiration. The pneumonitis that develops may be treated by the usual measures, oxygen and antibiotics. There are no specific antidotes.

Boric acid and borax (sodium borate) are common household chemicals intended either for use as an eye wash or an antiseptic solution, or to sprinkle around the borders near the door to discourage ants. There are many other uses. They are often put up in packages which are almost indistinguishable from the package of bicarbonate of soda. I have often wondered why we do not see more cases of boric acid poisoning. It seems to be so easy for a person who gets up in the middle of the night to take a dose of bicarbonate of soda to take in its place a teaspoonful of borax. It has no distinctive taste or smell. In spite of this cases of boric acid poisoning in the household are not numerous.

I had one inquiry about a person who swallowed about 4 ounces of a solution containing approximately 6 Gm. of boric acid. He vomited promptly. Such a dose in adults is not apt to cause serious injury and since he seemed to have emptied his stomach fairly well within a few minutes, the doctor was advised to do nothing about it. There was a follow-up in this case and it was established that it had caused no poisoning. I have here the record of another inquiry from a pediatrician. The mother made up the twenty-four-hour formula for her twins and she put 60 Gm. of boric acid into the solution in the place of one of the sugars. The error was discovered at the end of the day when all of it had already been given. It was estimated that about one-half of each feeding had been vomited so that each baby presumably retained 30 Gm. of boric acid. The babies were well forty-eight hours later without any treatment. That is much too long a time without symptoms after a toxic dose of boric acid. The toxicity of boric acid does not seem to be as great as is indicated by the statement found in the literature that 5 Gm. may be fatal to a baby and 15 Gm. to an adult. There must be very marked individual differences in susceptibility. There

is here in my folder another story about boric acid. The mother baked a cake and put in a teaspoonful of boric acid instead of baking soda. The baby ate a piece of the cake. Later in the day the mother discovered the error and telephoned to her pediatrician. He found nothing wrong with the baby. He was advised to do nothing about it. Nothing happened to this child but the mother had another question, namely, "Is the cake spoiled"? Apparently it was not as satisfactory a cake as it might have been if it had been made with bicarbonate of soda. I suggested that the cake was edible, but that it would not be wise to permit one member of the family to eat it all. The 5 Gm. of boric acid could do no harm when distributed among the members of the family.

I am, of course, speaking only of household accidents and not of errors of medication. You are undoubtedly aware of the disasters which have occurred in hospitals where boric acid was used in the place of sodium chloride for intravenous infusions. The occurrence of such accidents has created quite a furor in recent years. The question has been debated whether boric acid should not be colored to distinguish it more readily from harmless materials. The whole question of the utility of boric acid has been reviewed. There seems to be considerable doubt concerning its value as a medicinal agent and some hospitals have deleted it from their formularies.

Poisoning by boric acid causes fairly prompt gastrointestinal symptoms, such as vomiting, abdominal cramps, diarrhea, symptoms of circulatory collapse, coma or convulsions, skin eruptions, nephrosis and anuria. There is no specific antidote.

DR. JOHN B. DEITRICK: Would you say how you would treat poisoning by atropine?

DR. GOLD: I know of no specific antidotes to the fatal action of atropine. The only treatment is supportive, and the measures that one might use will depend on the symptoms which seem to be most threatening in the particular case. If the patient presents respiratory depression with cyano-

sis, one might use oxygen. If there is troublesome delirium or convulsions, one might quiet the patient by appropriate doses of barbiturates. Hyperthermia which may result from suppression of sweating can be managed by sponging. There are specific antagonists to atropine, such as prostigmine and mecholyl, but it is doubtful whether any safe doses of these can prevent the fatal action of atropine.

STUDENT: How about the use of pilocarpine?

DR. GOLD: The same applies to pilocarpine. It is extremely doubtful whether any amount of pilocarpine would counteract the fatal action of atropine.

DR. McKEEN CATTELL: The reverse would be all right, would it not?

DR. GOLD: Yes, atropine is a highly effective antidote against poisoning by the parasympathetic drugs. By means of atropine an animal can be saved from as much as ten times the fatal dose of physostigmine.

Dr. Helpern, you see a great many cases of poisoning in the Medical Examiner's Office. Would you tell us something about these?

DR. MILTON HELPERN: Those in the Medical Examiner's Office are, of course, fatal cases of poisoning. We encounter a large number of them in a year. Unfortunately, our department has no record of the non-fatal cases. There is no agency in the city through which the non-fatal cases are cleared. One would have to comb the hospitals and the records of private physicians in order to secure information on the total incidence of poisoning. A large proportion of the poisonings which we encounter are caused by ordinary household materials.

Illuminating gas is the chief cause of poisoning that we see. The toxic agent in it is carbon monoxide and the latter is responsible for more than one-half of all our cases.

The extermination of household pests provides a rich and varied source of household poisons. I might refer to a few of the more common ones which come to our attention. They are supplied under a wide

variety of trade names. There is the roach paste known as the John Opitz roach paste which is widely advertised. It reeks of yellow phosphorus. It is usually placed on pieces of potato or bread under the kitchen sink. Not infrequently the creeping child gets hold of one and munches on it. Since these preparations usually contain from 3 to 5 per cent yellow phosphorus, the child need only consume 1 Gm. or less to be seriously poisoned. He sometimes develops acute gastrointestinal symptoms which direct attention to the poisoning, but the effects may come on more insidiously with signs of acute hepatitis and often the poisoning is not suspected until irreversible symptoms have developed. Poisoning by yellow phosphorus in little children munching on fire crackers on the fourth of July is no longer a serious problem in communities where the use of fireworks has been controlled. There is the more commonly used roach powder which may represent almost pure sodium fluoride. Some protection against poisoning by this material is afforded by the recent law which requires the use of some distinctive dye, such as indigo, to color it blue. You may recall the report some time ago of the group of fatalities in an institution in Oregon where the cook confused the fluoride with flour. I might state that most of the fluoride poisonings which we encounter here are the result of attempts at suicide.

Rat poison is another exterminant which plays an important part in household poisonings. The most common agent is white arsenic. The preparation we have encountered comes in a little, round, wooden box, labeled "Poison." Perhaps the label is responsible for so many cases of suicide with arsenic. I recall one instance of homicidal arsenic poisoning in which a demented sister treated one brother with it on one day and the other the next day. The clinical picture, marked chiefly by gastrointestinal symptoms and collapse, is easily confused with other conditions and in the instance I just mentioned the diagnosis of botulism was made. It is unfortunate that physicians do not include poison-

ing more often among the possibilities when the diagnosis of an unusual disease is considered. I do not know of a case of suicide with arsenic in which the diagnosis was made during life. In the case of the two brothers which was just mentioned it is possible that a prompt and accurate diagnosis on the first boy might have prevented the second poisoning.

An insecticide which sometimes causes poisoning is one containing nicotine. These preparations contain about 40 per cent nicotine sulfate and are used as plant sprays. It causes nausea, vomiting, prostration and sometimes convulsions. It is rapidly fatal in doses of the order of about 50 mg.

Cleansing agents are another fruitful source of household poisonings. There are the strong alkalis, such as lye, concentrated ammonia and washing soda. Every so often baking soda is confused with washing soda and the concentrated sodium carbonate causes serious corrosion. Similar lesions are produced by lye and concentrated ammonia. Strong acids are sometimes found in the home, hydrochloric acid, sulfuric acid and nitric acid. We had a case of a child who drank the soldering fluid his father used when tinkering with electrical equipment. It is a concentrated mixture of zinc chloride and hydrochloric acid and it produced intense corrosion.

Dry cleaning fluids and stain removers are very common household poisons. The more common ones represent carbon tetrachloride, or mixtures of carbon tetrachloride, solvent naphtha, turpentine, benzene, gasoline and kerosene. Cases of poisoning result both from the inhalation of vapors as well as from ingestion. Some time ago we examined the body of a woman who had cleaned a dress with carbon tetrachloride in the bathroom, a small space without ventilation; she succumbed to the fumes of this compound.

Some potent metal cleansers contain cyanide. These solutions find their way into the home without proper labels. The cyanides are commonly used in silver polish.

Cyanide is very effective in taking tarnish off silver. It also lends itself to use for suicide. There used to be a preparation known as "Quick as a Wink" and another, "Cinderella" shoe polish, for cleaning metal finished shoes. One of these preparations suggested an antidote on the label, "If taken by mistake, throw cold water on the face." I suppose that was about as useful as any other.

The disinfectants commonly found in the home include such articles as tincture of iodine, carbolic acid, compound cresol solution (lysol) and creosote mixtures. Most of these produce not only systemic poisoning but local corrosive action as well.

I should not omit alcohol, the effects of which are well known. In this connection the solid wood alcohol mixtures such as Sterno and Dry Heat, present a much more serious problem. Alcoholics sometimes resort to these in extremity to prolong an intoxicated state. Rubbing alcohol and other medicated alcohols are also used for this purpose.

Black shoe dye often contains nitrobenzene. It is a potent poison. As little as 1 cc. may prove fatal although 30 cc. have been survived. It is readily absorbed through the skin of an infant's foot as well as by inhalation. It causes bizarre symptoms involving the gastrointestinal tract, the central nervous system and the viscera. Marked methemoglobinemia is an outstanding effect.

DR. GOLD: Dr. Dale is here from the Department of Pediatrics. It would be interesting to learn about the experiences of the pediatrician in this hospital.

DR. JOHN H. DALE, JR.: Our experience is in general agreement with your statement, Dr. Gold. A considerable proportion of the children admitted to this hospital present the problem of poisoning with household drugs, medications and other materials. Most of our patients are between two and three years old. The most frequent poison is fluoride roach powder. As a rule we see the children very soon after they have taken it. Gastric lavage is usually performed in the clinic. The signs and symptoms which

follow are those of gastro-enteritis and so far this has responded satisfactorily to bland diet and fluids. We recently saw a child who bit off the tip of a thermometer and swallowed the mercury. It passed through the intestinal tract in about three days and no signs of poisoning developed. The laxative known as Ex-Lax, which contains phenolphthalein, is another source of trouble for us. The usual story when they are brought in is that they have consumed from twelve to twenty-four of these chocolates. Except for purgation, nothing seems to have happened. One child that took some hydrochloric acid developed burns in the buccal mucosa and gastroenteritis. There was no bloody diarrhea. The recovery was uneventful. Children are commonly brought in with the story of having eaten a box or a book of safety matches. In view of the fact that the phosphorus is on the striking surface we considered it safe to send these children home without treatment. We have seen a few cases of lead poisoning, usually in children with hysteria or pica, who have taken to eating the paint on the stairs, window sills and elsewhere. These have been of the chronic, not of the acute, type of lead poisoning. This about sums up the chief types of cases which we encounter in this neighborhood. There have been no lye burns and no caustic poisonings of any kind.

DR. GOLD: Did most of the children that you have seen recover?

DR. DALE: All of them recovered. We have had no deaths from household poisonings in the past three years.

DR. GOLD: Even all the patients who took fluoride in the form of roach poison?

DR. DALE: Yes. Of course, we do not know how much was taken in these cases. The story is usually obtained from an extremely excited mother, and it is difficult to learn how much was taken but it seems that the children rarely take too much. Our experience bears out your point that overzealous treatment causes more trouble than the poison. As I stated we lavage the stomach with tap water and call it quits. We keep the child under observation for

changes in the pulse and for symptoms referable to the central nervous system. We treat gastro-enteritis with a bland diet. That seems to have been enough for our patients.

I might refer to the few cases which we have seen in which the child swallowed furniture polish. In these we have not been able to identify the toxic ingredients. Fortunately all of them recovered. We have seen two cases of acute alcoholism in children less than ten years of age. One of these could hardly be considered an accident since the family fed the child almost a pint of wine. The other was an eighteen month old infant who got his hands on a pitcher of beer and drank quite a bit of it. Both recovered.

When we go back further in the history of this department, we find some cases of poisoning by boric acid, hyoscine, atropine and codeine. Most of these were therapeutic poisonings. We have not had any of these in recent years.

DR. CATTELL: Might you have used calcium in the fluoride cases?

DR. DALE: We did not use it.

DR. GOLD: Are you referring to the value of calcium as a systemic antidote or for its effect in the gastrointestinal tract?

DR. CATTELL: I had in mind the fluoride in the stomach. The sodium fluoride would be converted into the extremely insoluble calcium fluoride if the stomach were washed with soluble calcium chloride.

DR. HELPERN: In your cases, Dr. Dale, was the fluoride recovered and identified by chemical analysis?

DR. DALE: No. We knew the brands of roach powder and the composition was supplied by the manufacturer.

DR. HELPERN: I ask this because fluoride is a very potent poison and it does not take very much of it to kill.

DR. GOLD: One has to take from 5 to 10 Gm. to produce serious poisoning in an adult. Most of the roach powders I think contain somewhere from 30 to 90 per cent sodium fluoride. In the case of the 30 per cent preparations one would need to con-

sume from 15 to 30 Gm. of the powder. That would be quite a meal.

DR. HELPERN: From what I have seen, Dr. Gold, one does not have to eat very much of it to get into trouble. I would recommend only very small doses of roach powder.

DR. GOLD: Dr. Dale, I surmise from what you have said about management of the cases in which a household poison has been taken that it is wise merely to wash out the stomach, observe the patient for a suitable time and then treat special symptoms as they arise, and that you refrain from the use of stimulants and depressants unless there is clear indication for them.

DR. DALE: That is the policy we have followed.

SUMMARY

DR. GOLD: The nature of the problems of household poisonings was explored in this conference. The number of chemicals which may be involved in household accidents is extremely large. No attempt, therefore, was made to exhaust the subject. The comments were confined to some of the more general aspects of the situations and to examples of some of the more common and interesting experiences. While there is fairly abundant information concerning poisons in the numerous texts on general toxicology, industrial toxicology, pharmacology and special articles in the medical literature, these often fail to provide the answers to the specific problems which the physician encounters in the case of a household accident. For example, information on the toxicology of mercury is abundant and readily accessible, but the case of the child who has bitten off the tip of the thermometer and swallowed it presents a special situation; the same is true for the toxicology of nicotine, but it does not quite cover the case of the child who has been munching on cigarettes. In such cases it would help to have at hand such facts as the chance of poisoning or the amount of cigarette tobacco babies are in the habit of eating.

Most accidental household poisoning

occurs in infants and young children who go exploring about in the home swallowing chemicals without discretion. There are such items as laxative pills containing strychnine; chocolate cathartics containing phenolphthalein; eye drops containing atropine; hypnotic capsules containing a barbiturate; matches; moth balls containing camphor, naphthalene or paradichlorobenzene; kerosene or gasoline; roach poisons containing phosphorus or fluoride; rat poisons containing arsenic; furniture polish and shoe dyes. These and a few others, such as borax taken accidentally in place of a dose of bicarbonate of soda, or put into a cake by mistake in the place of baking powder, or into the infant's formula in the place of sugar, received attention in the discussion.

Sodium fluoride is a violent poison but the pediatricians pointed out that while one of the common experiences at the New York Hospital is the case of the excited mother with the child who had been trying out roach powder containing sodium fluoride, they have encountered no cases of serious poisoning with this material in recent years although most of them received little or no treatment. There seems to be a wide gap between the accidental taking of a household poison and serious poisoning by it. Apparently the amount taken is usually too small. This is a matter of some importance for so often the real trouble is caused by overzealous treatment.

Unfortunately, many of the preparations containing poisons to which children are exposed in the home fail to provide the physician with a clue to the essential chemical. Opinion was strong in favor of extension of legal requirements for the appearance of the name of the compound on the label to guide the physician in appropriate measures, to allay panic and to prevent unnecessary treatment.

At the end of the session the problems relating to several other agents which participate in household poisonings remained in need of attention, also some of the more specific methods of treatment. These will be considered in a subsequent conference.

Clinico-pathologic Conference

Mediastinal Tumor with Gynecomastia and Superior Vena Caval Obstruction*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, J. S., (B. H. No. 158041), a thirty-four year old, white, married laborer, entered the Barnes Hospital on April 19, 1948, complaining of cough and shortness of breath. The family history was irrelevant. The patient had enjoyed excellent health most of his life, and systemic review revealed that aside from frequent upper respiratory infection he had had no serious illnesses. He had worked as a farmer for a number of years and subsequently was employed as a general laborer in a chemical plant.

Six months before entry to the hospital he was assigned to work in a portion of the chemical factory where he was exposed to sulfur fumes and almost immediately he began coughing. The patient stated that several other men who worked in the same section likewise complained of cough. His cough became almost continuous and was productive of a moderate amount of sputum which was occasionally blood-flecked. After two months he was transferred to the part of the plant in which he had worked originally but his cough persisted. Two months before admission he was examined by his private physician who found evidence of a mass in his chest. About the same time the patient developed dyspnea and orthopnea which progressed rapidly so that he was unable to lie flat without choking; as orthopnea became more severe the patient found it necessary to lean forward in order to breathe at all. He noted that his

head began to feel full, that the veins in his neck became prominent and that his right arm became swollen. His cough became so severe that occasionally after a paroxysm the patient lost consciousness for a matter of seconds. He developed persistent fever, his appetite decreased and he complained of abdominal fullness after eating only a very small amount of food. Eventually dysphagia appeared. In the month before admission to the hospital the patient's breasts increased in size; they felt hard but were not tender. His symptoms progressed and he became increasingly weak; following a series of laboratory and roentgenographic studies, which disclosed an increased basal metabolic rate, anemia, leukocytosis and a mass in the chest, the patient was advised to enter the Barnes Hospital. During the course of his illness he had lost 17 pounds.

At the time of entry his temperature was 37.5°C., pulse 94, respirations 28 and blood pressure 110/70 (right arm), 100/60 (left arm). The patient was a well developed but poorly nourished male who appeared acutely ill. He had great difficulty in breathing even though propped up in bed. Violent coughing was almost constant. He was able to breathe somewhat easier when he sat on the edge of the bed and leaned forward. The veins of the forehead, neck and right arm were tightly distended and there was some edema in those areas. The veins of the thorax were likewise dilated. Pallor of the skin and mucous membranes was

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

evident. Enlarged lymph nodes, which varied in size from 1 to 3 cm. in diameter, were felt in the cervical, left supraclavicular, axillary and inguinal regions. In the right infraclavicular region there was a mass 4 cm. in diameter which was thought to be possibly a lymph node. External examination of the eyes was not remarkable; there was no Horner's syndrome. Examination of the fundi revealed extreme fullness of the veins; the nose and throat appeared normal. The neck was swollen but soft, the trachea was in the midline and the thyroid was not palpable. The thorax was symmetrical and expansion was equal. About each breast there was a ring of discoid infiltration, approximately 3 cm. in diameter, which seemed firmly attached to the overlying skin. Examination of the chest revealed flatness to percussion extending 3 cm. to the left and 5 cm. to the right of the mid-sternal line anteriorly. Over this area tubular breathing was heard; similar breath sounds were heard at the right apex posteriorly. There were signs of fluid at the right base but no rales were audible. Except for tachycardia examination of the heart was within normal limits. The abdomen could not be examined adequately because the patient was unable to lie flat, but the liver edge apparently extended about 4 cm. below the right costal margin. The spleen could not be felt. The right testis was described as being atrophic; the left was not remarkable. Rectal examination was negative as was the neurologic examination.

Laboratory data were as follows: Blood count: red cells, 2,790,000; hemoglobin, 8.5 Gm. per cent; white cells, 12,300; differential count: stab forms, 5 per cent; segmented forms, 75 per cent; lymphocytes, 16 per cent; monocytes, 4 per cent. Urinalysis: negative. Stool: guaiac negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 16 mg. per cent; total protein, 6.3 Gm. per cent; albumin, 3.6 Gm. per cent; globulin, 2.7 Gm. per cent; cephalin-cholesterol flocculation test, 2+; icterus index, 6 units; thymol turbidity, 8 units; prothrombin time, 50 per cent

of normal; chlorides, 101 mEq./L., blood indices, within normal limits. Roentgenograms of the chest: films showed the heart to be essentially normal in size and shape. There was a large mass in the superior mediastinum extending further to the right than to the left, and there was evidence of fluid in the right pleural cavity. Small rounded areas of infiltration were scattered throughout both lung fields.

On the night of admission, the patient's respiratory distress became extreme. He obtained moderate relief by use of oxygen and sedation. The following day a biopsy was taken of the left breast. It was reported to show the histologic appearance of gynecomastia with hyperplasia of the ducts and proliferation of fibrous tissue. A presumptive clinical diagnosis of lymphoma was entertained but because of the patient's critical condition it was believed that a therapeutic trial with nitrogen mustard was merited. The patient received daily doses of 6 mg. of nitrogen mustard on four consecutive days; although considerable vomiting and malaise were associated with these treatments, the patient's dyspnea and orthopnea decreased. Coincident with clinical improvement further laboratory studies were undertaken. With the patient at a 45 degree angle, the venous pressure was 350 mm. of sodium chloride. The circulation time (arm to tongue with decolin) was 25 seconds. Following completion of nitrogen mustard therapy, the left supraclavicular node and the right infraclavicular mass decreased in size, but a chest film showed an apparent increase in the size of the mediastinal mass. On the twelfth hospital day the left supraclavicular lymph node was removed; microscopic sections showed almost total destruction of the lymphoid elements by an infiltrating carcinoma. The tumor cells were arranged in broad sheets and exhibited a tendency to gland formation. Abnormal mitoses were frequent and there were numerous nucleated tumor giant cells. The origin of the primary tumor could not be determined from the biopsy specimen.

Because of the gynecomastia, an Asch-

heim-Zondek test was performed and was reported to be positive. Although the patient had shown some symptomatic improvement, roentgen ray therapy was directed to the mediastinal mass with increasing dosage on consecutive days; a total of 3,800 roentgen units were administered. Following blood transfusions, the patient's red cell count rose to approximately 4,000,000. At the conclusion of x-ray therapy there was a slight decrease in the diameter of the retromanubrial mass, but the amount of fluid in the right chest had increased; the parenchymal infiltration of the lungs noted on admission remained unchanged.

During his last week in the hospital the patient complained of sharp pain in the region of the seventh and eighth ribs in the mid-axillary line, and marked rigidity in the thoracolumbar region of the vertebral column appeared. The testes were re-examined; although it was thought that both were rather atrophic, no tumor nodules could be detected. Shortly before discharge, the patient developed 3+ pitting ankle edema, and his red count fell to 2,800,000. Pain in the left chest persisted, and he required narcotics almost constantly for relief. During his hospital stay his temperature had remained elevated, sometimes being as high as 39°C. At the time of discharge on May 20, 1948, the right infraclavicular mass was noted to be further decreased in size, and the swelling of the neck and face had likewise decreased. The patient was referred to the tumor clinic for follow-up.

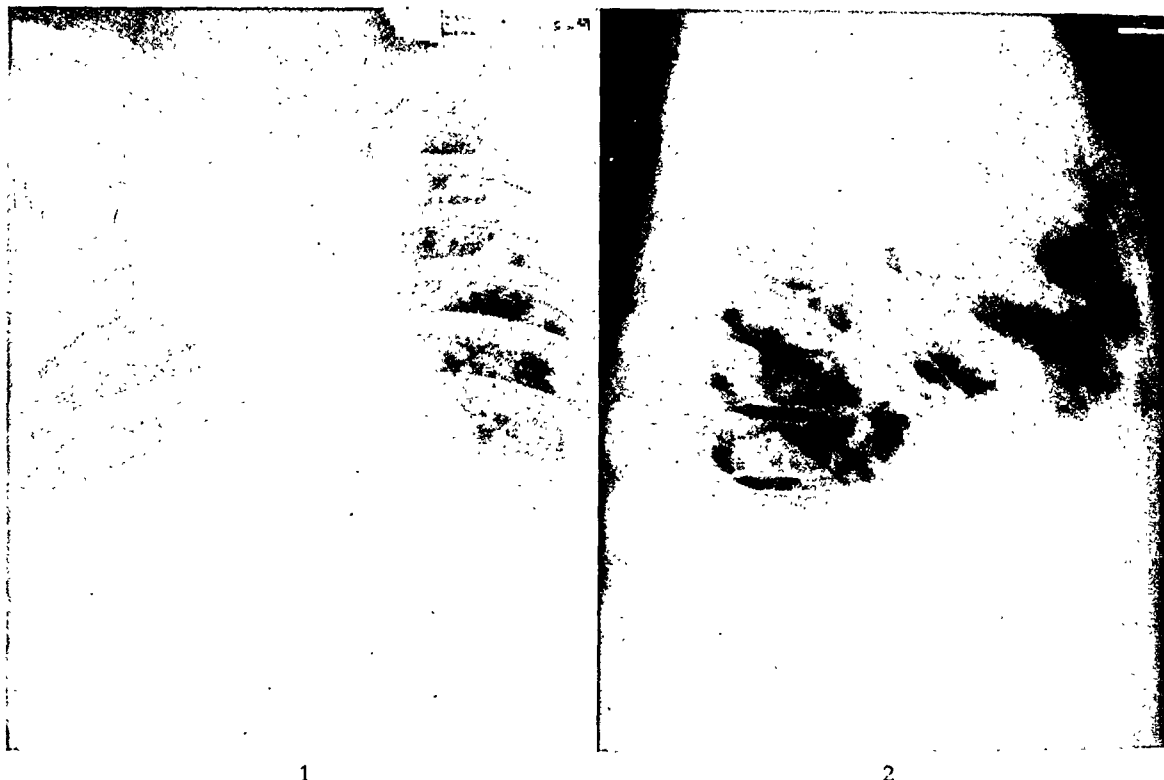
After leaving the hospital he continued to have pain in his left chest as he had had during his hospital stay. His cough re-appeared and once more paroxysms occurred during which time he lost consciousness. He produced occasional bloody sputum. Dyspnea progressed, abdominal swelling was noted and the patient complained of considerable epigastric discomfort. Gradually his feet again began to swell, the veins in the upper extremities and head again became distended and edema of the lower extremities increased; on June

1, 1948, he was re-admitted for the last time.

Upon admission his temperature was 37°C., pulse 104, respiration 32 and blood pressure 120/80. The patient was markedly emaciated. There was pigmentation of the skin over the regions to which roentgen ray therapy had been directed. The supraclavicular lymph node on the left and the infraclavicular mass on the right were markedly enlarged. Those in the axillary and inguinal regions were enlarged although not to the same degree. Venous engorgement of the face, neck and anterior thorax was marked. There was puffiness of the face, brawny edema of the right arm and hand and marked pitting edema of the lower extremities. Enlargement of the breasts was the same as on the previous admission. Examination of the lungs revealed signs of fluid at both bases, more on the right. Dry rales were heard at the right apex. Retrosternal dullness extended 6 cm. to the left and 6 cm. to the right of the mid-sternal line. The abdomen was distended, apparently with fluid. The liver edge extended 7 cm. below the right costal margin. As before the testes were small but no nodules could be felt. The remainder of the physical examination was as on the first admission.

Laboratory data were as follows; Blood count: red cells, 3,470,000; hemoglobin, 7.8 Gm. per cent; white cells, 12,640; differential count: eosinophiles, 2 per cent; stab forms, 12 per cent; segmented forms, 75 per cent; lymphocytes, 8 per cent; monocytes, 3 per cent. Blood chemistry: total protein, 5.2 Gm. per cent; albumin, 2.7 Gm. per cent; globulin, 2.5 per cent. The remainder of the blood chemical findings were unchanged from those reported previously. Quantitative Aschheim-Zondek test: negative for 0.5 cc. of serum, positive for 1.0 cc. of serum. Urine ketosteroids: 2.6 mg. for twenty-four hours; sodium pregnandiol glycuronidate; 19 mg. per twenty-four hours.

The patient's course in the hospital was progressively downhill and was charac-



1

2

FIG. 1. Chest film taken shortly after the patient was first admitted to the hospital. In addition to the large mediastinal mass, a number of small nodules are seen throughout the lung fields.

FIG. 2. Lateral view of the chest taken at the same time as Figure 1. Note that the mass lies high in the anterior mediastinum.

terized by increasing cachexia and weakness. At no time was he able to lie down, and for the most part he had to lean forward in order to breathe. He was given large doses of morphine for relief of pain. On one occasion a thoracentesis was performed, and 250 cc. of bloody fluid were removed. The fluid had a specific gravity of 1.020 and contained 2,100 leukocytes and 60 per cent polymorphonuclear forms. Culture of the fluid was sterile.

The patient expired quietly on June 17, 1948.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Dr. Bottom, would you care to discuss the chest films for us?

DR. DONALD S. BOTTOM: The first film (Fig. 1) was taken shortly after the patient's original admission to the hospital and it shows a number of interesting findings. A large mass may be seen in the mediastinum extending well into the right lung field and

to a lesser extent to the left. Throughout the lung there are a number of small areas of infiltration, all fairly well circumscribed. Furthermore, in the right pleural cavity a considerable amount of fluid is present. The lateral film (Fig. 2) indicates that the mass lies anteriorly.

The patient was sent to the x-ray department with the clinical diagnosis, "? lymphoma," and the x-ray diagnosis was returned, "? lymphoma." There are some reasons in retrospect which would lead one to question that diagnosis. In the first place the mass lay anteriorly in the mediastinum, and in that area teratomas, tumors of the thymus gland or substernal thyroids are much more common. Lymphoma, which would be more apt to involve the lymph nodes around the hilum, would not in all likelihood be situated as high in the mediastinum. Furthermore, when one reconsiders the small nodules scattered throughout both lungs, he realizes that it would be rather unusual to have that type of infil-

tration in lymphoma; rather, such masses are more typical of metastatic carcinoma. In retrospect, therefore, from a radiologic point of view a diagnosis of metastatic carcinoma would have seemed more suitable than one of lymphoma. Films taken after the completion of the course of x-ray therapy showed the mass to be smaller than it had been originally although the degree of change is not very marked. There was less fluid in the right pleural cavity. The metastatic areas in both lung fields, however, were more prominent than they were originally. A film taken during the second admission (Fig. 3) reveals that the mediastinal mass is considerably smaller than originally, but there is a rather large amount of fluid in both pleural cavities and a still further increase in the size of the metastatic nodules in the lung.

DR. ALEXANDER: This case is most unusual. From the report of the microscopic findings of the lymph node biopsy, it seems likely that this man had carcinoma with metastases which involved the lungs, mediastinum, lymph nodes and possibly the liver. Probably its most unusual feature was the association of gynecomastia, confirmed by biopsy. The origin of the tumor was not apparent to the surgical pathologists, and it is our problem to attempt to identify its primary site. Since gynecomastia does stand out as a striking finding, it would be well for us to review the mechanisms by which it may occur, and I shall ask Dr. MacBryde to comment.

DR. CYRIL M. MACBRYDE: In general, gynecomastia is associated with the presence of abnormally large amounts of estrogenic hormones in the male body. One of the most common causes of gynecomastia at present is the administration of stilbestrol in the treatment of carcinoma of the prostate. Presumably, estrogenic hormone in sufficient amount will produce enlargement of breast tissue in normal males. Unilateral gynecomastia may be seen after injury to one breast; local trauma to the breast can result in gynecomastia possibly because of alteration in the blood supply or because

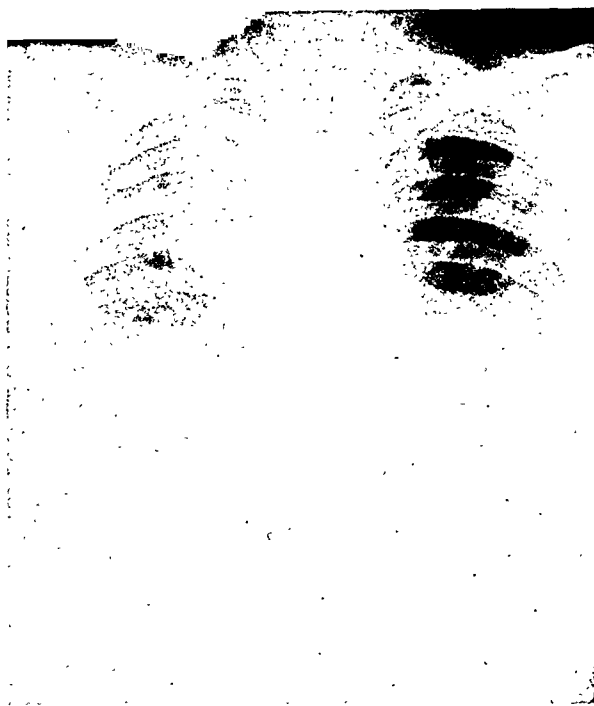


FIG. 3. Chest film taken during the patient's second admission. The mass is somewhat smaller but the amount of fluid in the pleural cavities has increased.

of sensitization of the tissues to amounts of hormones normally present. Gynecomastia is seen occasionally in newborn infants, both male and female; presumably, its occurrence under those circumstances is explained by the estrogen which was transferred to the body of the infant from the mother through the placenta. It usually disappears shortly after birth. Hypertrophy of breast tissue is seen in young boys at the age of puberty but the mechanism is not well understood; it is not a universal finding at that juncture. Gynecomastia occasionally occurs in older men who have a decrease in the production of testicular hormone. In regard to more serious conditions, gynecomastia appears in association with injury to the testes, with tumors of the testes and with certain diseases which result in atrophy of the testes. Cryptorchid testes seem to be particularly susceptible to the development of tumors with which gynecomastia may be associated. It also may be seen with any disease which leads to severe, diffuse liver damage, particularly cirrhosis. The cause usually advanced is that the liver

is unable to inactivate amounts of estrogen normally present in the male.

DR. ALEXANDER: Does gynecomastia occur in association with pituitary or adrenal disorders?

DR. MACBRYDE: Yes, rarely it may.

DR. ALEXANDER: On several examinations this patient was reported to have atrophy of both testes, but no tumor nodules were noted. Dr. Rouse, you saw this patient. Would you describe your findings?

DR. ERNEST T. ROUSE: Both testes were small, but both were definitely present. They were palpated repeatedly for tumor nodules, but none were ever detected. I did not believe that the degree of atrophy was remarkable.

DR. ALEXANDER: Although the patient had a 2+ cephalin-cholesterol flocculation test and an enlarged liver, I do not believe that there was liver damage to the extent necessary to explain gynecomastia on that basis. Dr. Wade, the Aschheim-Zondek test was reported as positive. Under what circumstances may a positive result be recorded other than with pituitary stimulation?

DR. LEO J. WADE: The Aschheim-Zondek test is normally positive during pregnancy and is associated with the appearance of large amounts of chorionic gonadotropic substances. The most common pathologic cause of a positive Aschheim-Zondek test is chorio-epithelioma which may give rise to enough chorionic gonadotropic substance to yield a positive test.

DR. ALEXANDER: Dr. Wood, I understand that you first suggested that this test be performed. Would you tell us your reasons for requesting the procedure?

DR. W. BARRY WOOD, JR.: Members of the house staff and others of us who saw this patient were very impressed by the gynecomastia. We believed as you did that the degree of liver involvement was not sufficient to explain it. Further, the patient had not been starved for a sufficiently long period of time in our opinion. In males one of the causes of gynecomastia is chorio-epithelioma, and for this reason we suggested to the house staff that an Aschheim-Zondek

test be obtained in an attempt to confirm that impression. When the positive results were made known, I consulted Dr. Robert A. Moore and told him that the patient had gynecomastia and a mediastinal mass. I asked him whether there could be any possible relation between the two, and he referred me to a paper on teratomas of the mediastinum in which Dr. H. G. Schlumberger, working in the Army Medical Museum, reported the results of a study of all the teratomas in the museum collection.¹ A number of cases of teratoma, instead of originating in the testis, arose primarily in the mediastinum. Having seen that paper, we became very much interested in the possibility that this patient had a primary teratoma of the mediastinum with a chorio-epithelioma which had metastasized and which had also caused the gynecomastia. That was our working hypothesis while the patient was in the hospital.

DR. ALEXANDER: Is it true that chorio-epitheliomas may produce enormous quantities of gonadotropic hormone?

DR. MACBRYDE: Yes.

DR. ALEXANDER: Dr. Moore, are metastases of chorio-epithelioma functional?

DR. ROBERT A. MOORE: In some instances metastases do produce chorionic gonadotropin. That depends in part on the maturity of the tumor. One cannot make a categorical statement, but I believe that it is generally accepted that cytotrophoblasts are the cells which produce chorionic gonadotropin. The cytotrophoblast is characteristic of the early stage of placental development which is the reason why the amount of gonadotropin produced is so high during the first month of pregnancy and then starts to decrease although in relative terms it is still high at the end of pregnancy. Chorio-epithelioma will duplicate the general structure of the placenta in every stage of its development. I can well imagine that at any given stage a metastatic nodule might produce small

¹ SCHLUMBERGER, H. G. Teratoma of anterior mediastinum in group of military age; study of 16 cases and review of theories of genesis. *Arch. Path.*, 41: 398, 1946.

amounts of hormone whereas another might produce huge amounts, depending on the relative number of immature cytotrophoblasts in the particular nodule.

DR. ALFRED GOLDMAN: There are cases reported in the literature in which, following removal of the primary teratoma, chorionic gonadotropin disappeared from the urine only to reappear when metastases from the original tumor became evident.

DR. ALEXANDER: That is a most interesting point, Dr. Goldman. When the Aschheim-Zondek test was done in this case, it was negative with 0.5 cc. of serum but was positive with 1 cc. of serum. Does that finding disturb you?

DR. WOOD: At the time we developed our hypothesis that report was not available; in retrospect, however, although those results are a bit disturbing, they do not make me believe that the diagnosis of chorio-epithelioma need be retracted.

DR. A. LEWIS FARR: It should be noted that the production of chorionic gonadotropin may be quite variable. It is usually stated in textbooks that the amount of gonadotropin produced by chorio-epitheliomas is extremely high. Dr. Willard Allen, however, studied a number of female patients with chorio-epitheliomas in whom production of gonadotropin was not significantly elevated.

DR. ALEXANDER: It is my understanding that the cause of gynecomastia in the male in the presence of excess estrogen. Is there any evidence that chorionic gonadotropin *per se*, gives rise to secondary female sexual characteristics?

DR. MACBRYDE: I do not believe that it alone can produce gynecomastia.

DR. ALEXANDER: Is it not true that gynecomastia is quite rare in males with chorio-epithelioma? I believe that in 1915 when Dr. J. V. Cooke reported the forty-seventh case, his was only the second in which gynecomastia was definitely described; in no other case was mention made of breast changes.²

² COOKE, J. V. Chorio-epithelioma of the testicle. *Bull. Johns Hopkins Hosp.*, 26: 215, 1915.

DR. MACBRYDE: Certainly all patients with chorio-epithelioma do not have gynecomastia.

DR. WILLIAM H. DAUGHADAY: The endocrine aspects of testicular tumors have been thoroughly reviewed by Twombly.³ He noted that there may be increased production of progesterone (as indicated by pregnandiol excretion), estrogens and of chorionic gonadotropin as well. Increased estrogen excretion was largely limited to patients with mixed epitheliomas rather than carcinomas. In five of eight such patients the excretion was moderately to markedly increased. There appeared to be a direct correlation between the amount of chorionic gonadotropin and increased estrogen excretion. Gynecomastia was associated with marked increase in urinary estrogen excretion.

DR. ALEXANDER: Dr. Wood, would you concede that the primary site of the tumor could have been in the testis, although it was too small to have been detected clinically?

DR. WOOD: Certainly.

DR. ALEXANDER: In summary, it seems that we agree that this patient had a chorio-epithelioma, probably primary in the mediastinum. Due to the limitation of time, we have been unable to discuss the superior caval syndrome, a classical example of which was seen in this man.

Clinical Diagnoses: Chorio-epithelioma; ?primary in mediastinum with generalized metastases; superior vena caval syndrome due to chorio-epithelioma of the mediastinum.

PATHOLOGIC DISCUSSION

DR. THOMAS L. YOUNG: At autopsy the body showed evidence of considerable weight loss. The skin was pasty gray in color. There was marked pitting edema of the legs and the left thigh and the neck veins were slightly distended. A few nodes

³ TWOMBLY, G. H. and PACK, G. T. Relationship of hormones to testicular tumors. In *Endocrinology of Neoplastic Diseases*. P. 228. Oxford University Press. New York, 1947.

were palpable in the left supraclavicular region. Both breasts were enlarged and beneath each nipple freely movable, firm masses, 3 cm. in diameter, were noted. There were also two small subcutaneous nodules just lateral and superior to the areola of the left breast.

There were 1,700 cc. of sanguineous fluid in the left pleural space and 1,100 cc. in the right. The lungs were studded with soft hemorrhagic, umbilicated tumor nodules, varying in size from a few mm. to 3 cm. in diameter. The pleural spaces about both apices were obliterated by dense fibrous adhesions. In the superior mediastinum encroaching on the apex of the right lung, the trachea, the superior vena cava and invading the azygos vein, there was a large mass 8 cm. in diameter; on cut section it was soft and variegated in appearance with many areas of necrosis and hemorrhage. Most of the tumor nodules in the lungs were hemorrhagic although on cut section some were yellowish brown, necrotic and friable.

In the abdomen the tumor surrounded the aorta and obliterated the vena cava and the iliac veins. In the region of the left adrenal there was a large, blue, soft mass which partially replaced the parenchyma of the gland, and numerous smaller tumors were scattered throughout the perirenal tissues. The lymph nodes in the abdominal cavity, including those in the peri-aortic and peripancreatic regions, were invaded by tumor tissue. In addition the tumor had extended retroperitoneally along the aorta, the vena cava and the renal vessels. A few nodules lay near but did not invade the ureters. The liver contained discrete, circumscribed, soft, cheesy, yellowish-white tumor masses varying in size from 0.5 to 4.0 cm. in diameter; only a few were hemorrhagic.

Both testes were atrophic, but in the right testis posteriorly a small firm nodule, 1 cm. in diameter, was palpable. On section the mass was found to be a cyst containing clear, colorless fluid. The left testis and epididymis were normal.

The brain weighed 1,560 Gm. The meninges were congested and a moderate cerebellar pressure cone was present; the unci of the temporal lobes were herniated slightly through the incisura tentorii. The ventricles were slightly dilated and a small mucoid cyst was present in the choroid plexus of the third ventricle. No metastases of the tumor were demonstrable in the brain. The pituitary was grossly normal.

DR. ROBERT A. MOORE: In this case the primary lesion was a tumor which involved many structures, including the mediastinum, lungs, liver, retroperitoneal lymph nodes and breasts. The tumor was soft and gray-red with numerous foci of hemorrhage; all of the nodules, however, were not converted into hemorrhagic masses such as are usually seen with chorio-epithelioma of the testis or mediastinum.

The first section (Fig. 4) illustrates the lobulated architecture of this tumor; a moderately dense connective tissue septum extends across the lower left corner of the field and in it are a moderate number of lymphocytes. Much of the tumor is necrotic as can be seen in the large focus on the right side of the photomicrograph. The tumor itself is not made up of a uniform type of cell; rather, it seems to follow a pattern as it were. In some areas of the section in Figure 4 two cell types may be distinguished; one group consists of large cells with moderately distinct cell borders, vacuolated or reticulated cytoplasm and nuclei which are highly anaplastic in appearance. In some of the nuclei, nucleoli may be seen. The second group of cells shows a good deal of variation. Some of the cells are quite dark with nuclei which are much more chromatic. The architectural pattern is such that the pale large cells are in the center and the smaller more chromatic cells are on the outside. Figure 2 is another view of the tumor in an area of necrosis. It illustrates the association of hemorrhage in close association with these same cells. In Figure 3 the two cell types are seen under higher magnification. At the left of the section a number of pale large cells with

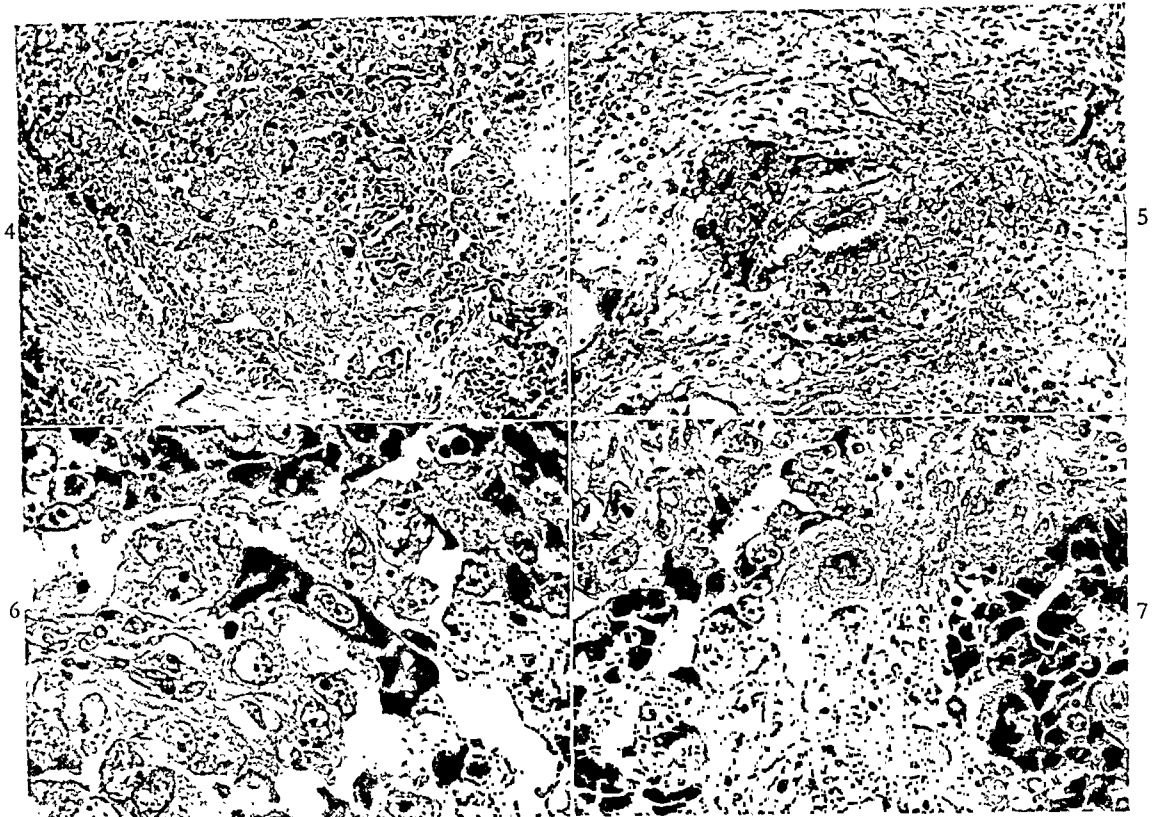


FIG. 4. Metastatic chorio-epithelioma showing the lobulated architecture and a focus of necrosis.

FIG. 5. Hemorrhage and necrosis in close association with the cells of the tumor.

FIG. 6. Cell types within the tumor illustrating the large pale cells with vacuolated nuclei and darker cells with more chromatic nuclei.

FIG. 7. Detailed illustration of the large syncytiotrophoblastic cell and an abortive chorionic villus to the left of center.

vacuolated nuclei are seen; on the right the cells exhibit basophilic cytoplasm and more chromatic nuclei. A detailed view of the large cell type is seen in Figure 4. The cell wall is irregular, there is fine vacuolation and some basophilia of the cytoplasm and the cell is multinucleated. It may be noted that the tumor is characterized by cellular masses in which a large pale cell is surrounded by more chromatic smaller cells.

There can be no question that this tumor is a chorio-epithelioma for it exhibits all of the essential characteristics. There are aborted, very early chorionic villi made up of a cytotrophoblast surrounded by syncytiotrophoblasts. The syncytiotrophoblasts have the typical appearance of those seen in the placenta from the eighth to tenth days of human gestation; it is at this time that these cells produce more chorionic gonadotropin than they do at any other

stage of development and maturation. This tumor, which may also be called a choriocarcinoma, duplicates the structure of the placenta. It has a tremendous proclivity for invasion of tissue over and above that which the trophoblastic cell shows in invading blood vessels in the normal placenta.

Let us now consider the fact that in the male chorio-epithelioma may occur primarily in any one of three places: It may arise in a testicular tumor, in the mediastinum or in the region of the pineal body. These three sites may be properly grouped under two headings: gonadal and extragonadal, the tumors arising in the mediastinum and the region of the pineal body being classified together as extragonadal. It is relatively simple to explain the origin of any totipotent tumor cell if it occurs in the gonad but it is more difficult to explain its occur-

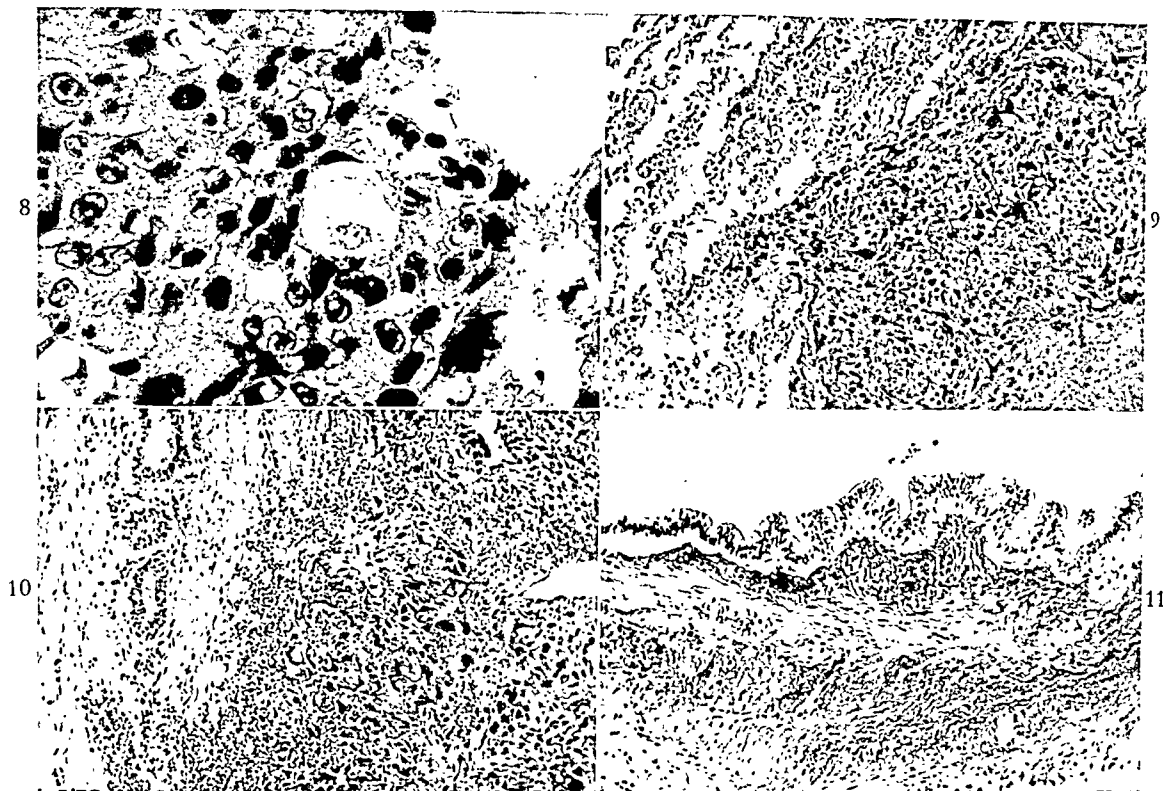


FIG. 8. Metastatic tumor in the liver with the typical architecture of a chorio-epithelioma.

FIG. 9. A section showing metastatic tumor in the lung.

FIG. 10. Section of the breast with changes of gynecomastia on the left and metastatic chorio-epithelioma on the right in a single field.

FIG. 11. Cyst in the wall of the testis. Note that the cells lining the cyst wall are of the tall columnar type characteristic of the alimentary canal. The lamina propria and muscularis are seen underlying the epithelial layer.

rence outside the gonad. It is important to remember, however, that both of the extragonadal sites of origin are in the mid-line; it seems quite likely that totipotent cells which retain their capacity to produce both trophoblastic and somatic cells are isolated in the blastophore stage of the embryo and come to rest in either of these two sites.

To illustrate further that this tumor was a classical chorio-epithelioma Figure 5 shows a metastatic lesion in the liver; again, there are cytotrophoblasts and syncytiotrophoblasts in typical relation to one another. Figure 6 is a section of the lung in which another metastasis is seen; again, the orientation of the two cell types is typical.

Figure 7 is a section of the breast which confirms the diagnosis of both gynecomastia and metastatic chorio-epithelioma. On the left hyperplasia of the epithelium, thicken-

ing of the periductal tissue and slight periductal cellular infiltration are seen; on the right metastatic chorio-epithelioma is apparent.

Dr. Young described a cyst in the testis 1 cm. in diameter and Figure 8 is a section from the wall of the testis showing a cystic space lined with tall columnar epithelium of the type seen in the alimentary canal; beneath the epithelium smooth muscle may be seen.

In view of this finding I believe that a diagnosis of teratoma of the testis must be made and this case assumes great importance in regard to our concepts of the nature of testicular tumors; it represents one of eight or ten in the literature in which there is association of a true adult teratoma of the testis and metastatic chorio-epithelioma although to find a teratoma of the testis that has some other elements in it and

metastatic chorioepithelioma is not unusual. If I propose to you that at some earlier date this patient had a malignant tumor of the testis which metastasized and that subsequently the primary tumor became benign, it will involve some theorizing concerning the nature of testicular tumors. However, I would like to attempt to support just that concept. I think it is becoming increasingly evident that nearly all testicular tumors are of one type although they may show some cellular variations which influence their prognosis. The basic fact in regard to tumors of the testis is that they are derived from a sex cell which probably undergoes parthenogenesis during the course of development of the tumor. Now if indeed such a series of circumstances occur, two cell types may result, namely, trophoblastic and somatic cells. In the normal course of pregnancy the trophoblastic cells become the adult placenta and are discarded at the end of the period of gestation; the somatic cells develop into the organism. A comparable chain of events occurs in testicular tumors. My own hypothesis, which has been accepted and propounded independently by others, is that all testicular tumors go through a phase in which they contain malignant trophoblastic tissue as well as somatic tissue. In some instances the somatic element is lost and eventually only chorio-epithelioma remains. In other instances the trophoblasts are lost and only the somatic portions remain so that an adult teratoma develops. If during the earliest period of development of such a tumor a few trophoblastic cells escape, they may develop into a chorio-epithelioma at a distant site although in the primary site the trophoblasts may disappear and leave only somatic cells to form a benign adult teratoma. I think such a sequence of events occurred in this case. Another possibility which seemed likely when we first examined the testis and found a nodule is even rarer than the one which I have just discussed, namely, that the primary tumor develops from one of the trophoblastic cells, but for some unknown reason it undergoes

fibrosis and destruction and ultimately is represented by only a scar. I have seen two such cases in the series that I studied.

I would like to comment briefly on the subject of hormone production by tumors for I think it is most important to correct some of the false impressions concerning the presence of gonadotropin in the urine. In patients with all types of testicular tumors there is an increased amount of gonadotropin, but if an examination is made to distinguish between hypophyseal gonadotropin, originating presumably from the basophilic cells of the pituitary, and chorionic-gonadotropin, originating from cytotrophoblasts, it will be found that hypophyseal gonadotropin is increased in every patient with a testicular tumor. Certain patients with tumors of the testis have in addition large amounts of chorionic gonadotropin and surgical excision of the tumor or its destruction by radiation in no way influences the hypophyseal gonadotropin but merely removes the source of chorionic gonadotropin. The divergence of opinion in the literature concerning the effects of operation on gonadotropin excretion results from the failure to consider the nature of the determination performed; some workers have measured hypophyseal gonadotropin whereas others have determined chorionic gonadotropin. Thus, with more sensitive tests it has been reported that removal of the tumor had no effect on gonadotropin excretion, whereas with relatively insensitive tests which are commonly employed in most laboratories excellent results have been obtained which show that gonadotropin is present before operation but disappears afterward. If this phase of the problem is to be clarified, a sensitive procedure is essential; if that is done, it is found that the only two tumors of practical importance which produce chorionic gonadotropin are the embryonal carcinoma and chorio-epithelioma. Patients with adult teratomas do not excrete increased amounts of hypophyseal gonadotropin as do all patients with testicular tumors.

Finally, concerning gynecomastia, I do

not know that anyone has put forward evidence as to why some patients with chorio-epithelioma have gynecomastia and others do not. I would reason that the estrogen producing gynecomastia comes from the chorionic cell and I think that if one carefully examined the cells of the tumors in those with gynecomastia, one might be able to determine which cellular element or architectural pattern is present only in such patients and absent in those without gynecomastia.

Anatomic Diagnoses: Adult teratoma in the right testis; metastatic chorio-epithelioma in all lobes of the lungs, liver, breasts, subcutaneous tissues of the left thorax, pelvis of the right kidney and the left adrenal

gland, and in the iliac, peri-aortic, peri-pancreatic and anterior and posterior mediastinal lymph nodes; extension of chorio-epithelioma into soft tissues of the mediastinum with invasion of the superior vena cava and azygos vein and the wall of the trachea; chorio-epithelioma involving the retroperitoneal connective tissue about the aorta, inferior vena cava, renal pedicles and ureters; gynecomastia, bilateral.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Editor's Note: Reprints of these conferences are now available. Requests should be sent to Dr. Robert J. Glaser, Department of Medicine, Barnes Hospital, St. Louis 10, Mo.

An Unusual Case of Clonorchiasis with Marked Eosinophilia and Pulmonary Infiltrations*

GEORGE E. CARTWRIGHT, M.D.

Salt Lake City, Utah

A CASE of clonorchiasis with marked eosinophilia in the peripheral blood and bone marrow and bilateral pulmonary infiltrations is presented. The similarity and possible relation of this condition, Löffler's syndrome and tropical eosinophilia (eosinophilic lung) is discussed.

The case presented is of interest for several reasons:

1. Clonorchiasis in army personnel has not been rare. It has been encountered frequently in the China-Burma-India theater. During the winter of 1945 to 1946 a number of patients with leukocytosis, marked eosinophilia and carrying ova of *Clonorchis sinensis* in the feces were observed in an Army general hospital in Shanghai, China. Heretofore this condition has received very little attention within the United States. The problem will be of importance in returning military personnel, not only from the China theater but also from Korea and Japan. It will now have to be considered in patients presenting marked eosinophilia and the diagnosis, even in experienced hands, is many times difficult. In many cases the ova can be demonstrated only after repeated stool and bile examinations.¹

2. As far as the author is aware no cases of clonorchiasis with pulmonary infiltrations have been recorded in the literature. This enlarges the growing list of etiologic agents in the production of the so-called Löffler's syndrome.

3. The reported cases of clonorchiasis in which the blood changes have been followed over such an extended period of time are few.

4. The similarity between this condition and tropical eosinophilia (eosinophilic lung) gives rise to several interesting problems.

Clonorchiasis is caused by the presence of the Oriental liver fluke, *Clonorchis sinensis*, in the biliary passages.^{1,3} This fluke occurs in the Far East as a common parasite of fish-eating mammals. The highly endemic regions of human infection are China, French Indo-China, Japan and Korea. The life cycle requires about three months. Man, dogs and cats serve as reservoir hosts. The eggs, laid in the smaller bile passages, are carried down the common bile duct to the duodenum and are passed in the stools. The ova must reach water and are believed to hatch when ingested by appropriate species of snails. Development within the snail requires four to five weeks and includes the production of mother sporocysts followed by a generation of rediae. At the end of this interval cercariae break out of the rediae and emerge from the snail. These cercariae penetrate beneath the scales and into the musculature of fresh water fish where after a developmental period of several weeks they produce cysts. After ingestion of raw or poorly cooked fish by man or other suitable mammalian hosts the cysts are digested and the

* From the Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah.

parasites are released in the duodenum where they become attached to the mucosa. They soon migrate through the papilla of Vater into the common bile duct and then into the smaller biliary radicles, especially those of the left lobe of the liver. Pathologically, clonorchiasis is characterized by proliferation of the biliary epithelium, connective tissue hyperplasia and, in severe prolonged cases with repeated infections, by fatty degeneration, eosinophilic infiltration and cirrhosis of the liver.⁴ The majority of infected persons harbor few worms and do not present significant symptoms.⁵ A few patients develop edema, diarrhea and hepatomegaly. The most advanced cases are associated with cirrhosis of the liver, anasarca, cachexia and extreme jaundice. No satisfactory treatment has been found. Gentian violet medicinal administered orally is recommended for heavy infections of long-standing. The disease runs a self-limited course in asymptomatic patients with light infections.

CASE REPORT

A white male, aged twenty-one, entered the orthopedic service of a general hospital in Shanghai, China, on April 7, 1946, complaining of intermittent low backache.

Three years previously he had been kicked low in the back by a horse, following which he was in bed for three weeks with low back pain. Since that time, he had had intermittent pain brought on by jolting rides, stooping and weight lifting. On the day prior to admission, following a severe jolting ride in a truck, the pain became severe, especially upon stooping, and he was confined to bed. The pain did not radiate, was localized over the lumbar area and was not accentuated by coughing or sneezing.

The past history revealed that the patient arrived in India in February, 1945. Shortly afterward he developed a mild, productive cough and noticed "bronchial wheezing" especially at night. These symptoms were never severe. On December 22, 1945, he attended a banquet in Kunming, China, and ate poorly cooked native fish. Three months later he developed a bilateral conjunctivitis which lasted two weeks.

The patient gave a history since the age of 13 of numerous attacks of "hives" supposedly due to oranges, tomatoes and strawberries. He had had about twelve attacks of hives in the previous ten months although he had rarely eaten oranges, tomatoes or strawberries. The attacks were relieved by adrenalin and calcium. There was no other history of allergy. He was treated for amebic dysentery in May, 1945. He gave no history of diarrhea since that time.

The family history revealed that the patient's mother frequently developed hives following ingestion of tomatoes. There was no other family history of allergy.

Physical examination disclosed the following: Temperature, 98.8°F., pulse, 82; respiration, 16 and blood pressure, 122/84. The patient did not appear ill. He was somewhat obese with a rather marked lordosis and protuberant abdomen. The conjunctivae were moderately injected bilaterally. The sclerae were not icteric. The color of the mucous membranes was normal. There was slight tenderness on deep palpation over the mid-lumbar spines, the sacrospinalis muscles and both costovertebral angles. There was no glandular enlargement. The liver and spleen were not palpable. The remainder of the physical examination, including examination of the chest, was not remarkable.

Laboratory data revealed the following: Kahn, negative; hemoglobin (Sahli), 16 Gm. per cent; sedimentation rate, 18 mm. per hour; volume of packed red cells, 42 cc. per 100 cc., white cell count, 10,000 per cu. mm. Differential count: metamyelocytes, 2 per cent; neutrophils, 48 per cent; eosinophils, 20 per cent; lymphocytes, 26 per cent; monocytes, 4 per cent. Routine examinations of the urine including microscopic examination were unremarkable. A urine culture was sterile. The non-protein nitrogen of the blood was 34 mg. per cent. A Mosenthal concentration-dilution test was normal (1.025 to 1.003 specific gravity). An intravenous pyelogram failed to reveal any abnormalities. X-rays taken of the lumbosacral spines and pelvis were not remarkable. Repeated stool cultures failed to reveal the presence of a pathogenic organism. Twenty-four stool examinations for parasites and ova were negative. No significant abnormalities were noted on proctoscopic examination.

Intracutaneous skin tests were performed with thirteen inhalant allergens, seventeen food allergens, two pollens and two molds, with the



FIG. 1. A, roentgenogram of the chest taken on May 1st showing bilateral lower lung field infiltrations; B, roentgenogram taken on May 6th. There has been noticeable resorption of the process in the left lower lung field; there has been little change on the right; C, roentgenogram taken on May 13th. There has been further resorption on the left but still no significant change on the right; D, roentgenogram taken on June 10th. There has been complete clearing of the infiltrative process in both lung fields. The bronchial markings are somewhat increased.

following positive results: rice, 3 plus; house dust, 3 plus; cow, 2 plus; feathers, 2 plus; yeast, 2 plus; orris, 1 plus; pyrethrum, 1 plus; corn, 1 plus; tomatoes, 1 plus. No sensitivity was found to oranges.

The back pain subsided completely upon heat, rest, acetylsalicylic acid and use of a backboard. On the second hospital day (April 9th) he had a mild shaking chill and the temperature rose to 100.4°F. (oral). A blood smear for malaria was negative. Thereafter the oral temperature fluctuated between 98.0 and 99.2°F. On April 30th the per cent of eosino-

phils had risen to 65. The white cell count was 7,600 per cu. mm., the sedimentation rate (Wintrobe hematocrit tube) 17 mm. per hour and the volume of packed red cells 42 cc. per 100 cc. The patient was transferred to the medical service for an investigation of the low grade fever and eosinophilia. On May first examination of the chest revealed dullness to percussion with decreased tactile fremitus and decreased breath sounds over the left lower lung field posteriorly. The roentgenogram (Fig. 1) showed an area of moderately increased density covering the entire left lower lung field below

the eighth rib posteriorly and a small area of moderately increased density located in the sixth right anterior interspace. There were no symptoms, pulmonary or otherwise, at the time. The sedimentation rate was 19 mm. per hour and the cold agglutination titer was not

generalized moderate increase in density with an increase in the bronchial markings. The patient developed a mild cough productive of small amounts of yellowish-mucoid sputum. A smear of the sputum stained with Wright's stain revealed that about 50 per cent of the cells

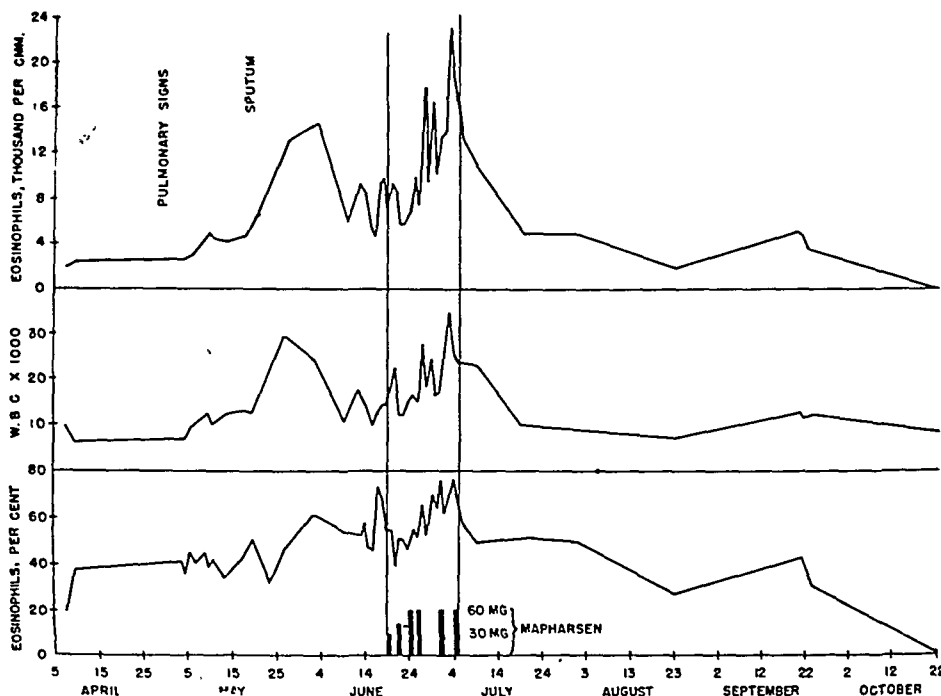


FIG. 2. Showing the effect of mapharsen on the leukocyte count and absolute and relative eosinophilia.

diagnostic. Blood cultures were repeatedly sterile. Typhoid "H" and "O" and paratyphoid A and B agglutinations were not significant. A roentgenogram of the chest taken on May 10th revealed clearing in the left lower lung field but there was no change in the density in the right lower lung field. (Fig. 1B.) By May 13th the left lower lung had cleared still more but the bronchial markings were quite dense. The area of density in the right lower lung was unchanged in size and also seemed to follow the pattern of the bronchioles. (Fig. 1C.) There was no rise in the cold agglutinin titer. Repeated blood cultures were sterile. Between the 8th and 12th of May the temperature fluctuated between 99.0 and 100.0°F. Examination of the chest during this time was not remarkable. There was slight leukocytosis (10 to 13 thousand per cu. mm.) and the eosinophiles fluctuated between 39 and 54 per cent. The eosinophiles were principally normal adult cells with an occasional stab cell. No myelocytes or abnormal cells were seen in the blood smear. On May 20th the lower lung fields bilaterally showed a

were eosinophiles. The cough persisted. Physical examination of the lungs again failed to reveal any abnormalities. By May 27th a noticeable resolution had taken place as seen in the roentgenogram. By June 3rd almost complete resorption of the infiltrative process had taken place. The bronchial markings over both lower lung fields remained moderately increased. The cough disappeared and the patient was asymptomatic and afebrile. The white cell count had risen to 24,400 per cu. mm. and the per cent of eosinophiles to 62. The eosinophiles were again adult cells with an occasional band form. No myelocytes or blast cells were seen. Between the 3rd and the 19th of June the white cell count varied between 10,000 and 17,000 per cu. mm. The eosinophiles fluctuated between 45 and 74 per cent. During this period there was complete resolution of the process in both lung fields. The bronchial markings in the right lower lung field were still somewhat increased. (Fig. 1D.) Repeated examinations of fresh specimens of stool were negative for ova and parasites. Aspiration of the sternal marrow on June 7th,

at which time the total white count was 24,200 per cu. mm. and the per cent of eosinophiles was 62, revealed the following information: Myeloblasts, 1.0; promyelocytes, 4.0; eosinophilic myelocytes, 4.0; eosinophilic metamyelocytes, 10.0; eosinophiles, 32.0; neutrophilic metamyelocytes, 5.0; neutrophils, 15.0; lymphocytes, 16.0; monocytes, 2.0; normoblasts, 9.0; megakaryocytes, 1.0; basophiles, 1.0.

Mapharsen therapy was begun on June 19th. The patient received six intravenous injections (0.31 Gm.) over a sixteen-day period. (Fig. 2.) There was a marked rise in the total white count to 34,900 per cu. mm. and the eosinophiles fluctuated between 40 and 76 per cent. On July 1st ova of *Clonorchis sinensis* were demonstrated for the first time in the stool. Many ova were seen. This was the twenty-fifth stool examination. Many ova of *Clonorchis sinensis* were again seen on the following day. By the time the mapharsen therapy had been completed (July 4th) the white cell count and per cent of eosinophiles had begun to fall. During the next three months the white cell count gradually decreased to normal and the eosinophiles diminished to 2 per cent. During this time the patient was afebrile and entirely asymptomatic. Physical examination of the lungs was not remarkable. Stereoscopic films of the chest taken on September 10th were negative. Ova were never again demonstrated in the stool and two examinations of the bile were negative for ova. At no time during the course of the illness was diarrhea present.

Summary. This patient entered the hospital with a complaint of low back pain which was irrelevant to the condition under discussion. On admission an eosinophilia of 20 per cent was present. He was asymptomatic except for the initial complaint. During the hospitalization he developed chills, an intermittent low grade fever and clinical and roentgenologic evidence of bilateral pulmonary infiltrations. The physical signs were fleeting but the infiltrations were slow in resolving. Following detection of the pulmonary lesions, he developed a cough productive of small amounts of sputum containing many eosinophiles, as well as leukocytosis associated with an increase in the eosinophiles in the peripheral blood to 74 per cent. A differential count

on the bone marrow obtained following sternal puncture revealed that 46 per cent of the cells were eosinophiles. Following mapharsen therapy, there was an initial increase in the eosinophilia and leukocytosis which was followed by a gradual decline to normal over the course of several months. Diarrhea was not a feature of the illness. The ova of *Clonorchis sinensis* were demonstrated in two consecutive stool specimens. The patient was not particularly ill at any time; indeed, there was a paucity of clinical symptoms and signs.

The difficulty in the diagnosis of clonorchiasis is well illustrated in this case. The first twenty-four stool examinations were negative. It is difficult to state with certainty when the original infection occurred. To the patient's knowledge the only time he had eaten local fish was on December 22, 1945. Whether the mild pulmonary symptoms which he experienced in India in the early part of 1945 were a part of his illness or a separate one is not known. The symptoms were not severe enough for him to request a medical examination at the time. It is interesting that he had a history of previous allergy and that there was a familial history of allergy to a limited degree. What relation this had, if any, to the patient's symptoms and signs is impossible to state.

COMMENTS

Leukocytosis and eosinophilia have been noted in both experimental^{6,7} and human clonorchiasis. A significant eosinophilia and marked leukocytosis are present in most Koreans infected by *Clonorchis sinensis*.¹ Bercovitz¹ has reported an eosinophilia as great as 48 per cent and a leukocytosis as high as 31,600 per cu. mm. An eosinophilia (10 to 47 per cent) but not leukocytosis has been reported in infected Chinese.⁵ In Japan it is stated that clonorchiasis is accompanied by leukocytosis but eosinophilia has been observed in only about 24 per cent of the cases and then it is never marked.^{8,9} It would seem that the degree of leukocytosis and eosinophilia varies some-

what according to the race of the host. As further evidence of this during the winter of 1945 to 1946, a number of German patients with fever, jaundice, leukocytosis (10,000 to 30,000), eosinophilia (20 to 80 per cent), pulmonary infiltrations and ova of *Clonorchis sinensis* in the stools was observed by the writer in a repatriation camp in Shanghai. This, along with the observations made upon American soldiers in China, suggests that in races with little previous exposure the leukocytic and eosinophilic response may be greater.

The clinical syndrome described here fulfills the diagnostic criteria of the syndrome described in 1932 and again in 1936 by Löffler,^{10,11} namely, a mild clinical course, transient pulmonary signs, characteristic pneumonic infiltrations roentgenographically, eosinophilia and leukocytosis. Löffler described the roentgenograms as showing homogenous or more often spotty or cloudlike, sharply or less sharply limited, single or multiple, unilateral or bilateral, migratory shadows that appeared and disappeared in three to eight days. Since his original description, cases have been reported in which the pulmonary lesions have persisted longer than eight days. Wright and Gold¹² report that in Löffler's syndrome associated with creeping eruption the pulmonary infiltrations continue over a period of weeks if the cutaneous lesions are not treated. It is now generally agreed that Löffler's syndrome is an allergic phenomenon.¹³ The etiologic factors which have been reported are chronic asthma, tuberculosis, coccidioidmycosis, privet shrub pollen in China, pollen of the *Convallaria* in Europe, *Ascaris lumbricoides*, *Trichuris trichuria*, *Strongyloides stercoralis*, *Taenia saginata*, *Fasciola hepatica*, *Endamoeba histolytica*, *Trichinas*, cutaneous helminthiasis, brucellas and azosulfamide.^{12,13} From the observations reported herein it would seem that *Clonorchis sinensis* may now possibly be added to the list.

In India during the past six years there has been a growing interest in the recently recognized and commonly occurring con-

dition described as tropical eosinophilia, eosinophilic lung, pseudotuberculosis of the lung with eosinophilia and benign eosinophilic leukemia.¹⁴⁻¹⁹ Clinically, the disorder is variable and the mode of onset is gradual. In the acute stage there is usually fever, a dry hacking cough and symptoms of asthmatic bronchitis. Severe paroxysmal bronchial asthma may develop. Asymptomatic cases have been described. Physical signs when present are those of a mild bronchitis. Splenomegaly and enlargement of the lymph glands may be present but neither are a constant finding. Roentgenograms usually reveal numerous discrete shadows scattered throughout both lungs producing a typical mottled appearance. The sputum when present contains eosinophiles. The most characteristic finding of the syndrome is in the blood. There is a leukocytosis of 20,000 to 80,000 per cu. mm. and the eosinophiles vary from 15 to 90 per cent of the total white cells. Considerable fluctuation of the absolute eosinophile count from day to day has been noted.¹⁹ There is no correlation between the blood findings and the clinical or radiologic pictures. Positive serologic tests for syphilis and high cold agglutination titers have been present frequently.^{20,22} The duration of the illness has varied from a few weeks to a few years. The most characteristic feature other than the eosinophilia is the response to organic arsenical therapy. Neoarsphenamine given every fourth day in a course of six (0.15, 0.3, 0.45, 0.45, 0.45, 0.45) injections is highly effective. After the first two or three injections there is usually a rise in the total leukocyte count and in the percentage of eosinophiles. This has been considered by several authors to be diagnostic of the disease.^{19,21} The rate of the return of the blood to normal varies but a fall in the leukocyte count and in the percentage of eosinophiles is noted in two to four weeks and usually reaches normal in two to four months. Oral arsenical preparations are equally effective. The disease has now been reported from not only India but also Ceylon, China, America, Havana, Egypt,

Samoa, the East Indies and the Netherlands West Indies.²¹ The etiology is in dispute. Mites (acarina) have been repeatedly found in the sputum of patients by some observers and a relation between these and the etiology of the disease has been claimed.²³⁻²⁵ Others have been unable to confirm this.¹⁹ *Strongyloides stercoralis*²⁶ and *Microfilaria malayi*²⁷ have been believed to be the etiologic factors in several cases. No particular infestation has been consistently present and in many cases no parasites or ova have been found after repeated blood and stool examinations. Concerning the etiology of this condition, Frimodt-Møller and Barton¹⁴ state "In conclusion, it may be said that much in this clinical entity points to an allergic origin, chiefly because the eosinophilia dominates the syndrome described. But it is possible that there may not be a single agent which causes such a condition, but several."

Eosinophilic lung as described in the literature differs from Löffler's syndrome in several respects. The former disease is usually of longer duration, the symptoms are more marked, the total leukocyte count and the percentage of eosinophiles are usually higher and the pulmonary lesions are more diffuse. Actually these are differences only in degree and it is debatable whether tropical eosinophilia and Löffler's syndrome are actually different diseases. In fact, van der Sar²⁵ has noted mite infection manifesting itself as tropical eosinophilia in some cases and as Löffler's syndrome in others.

The patient presented here fulfills the diagnostic criteria of both syndromes, further suggesting that there may be no fundamental difference between them. The clinical course and roentgen findings were more characteristic of Löffler's syndrome whereas the extremely high absolute eosinophilia and the response to organic arsenical therapy, with first a rise in the absolute count followed by a fall to normal are, according to Menon,²¹ almost diagnostic of tropical eosinophilia. He states "If the total eosinophile count is 5,000/cu. mm.

and above, i.e., 25 per cent and more of a total white cell count of 20,000/cu. mm., tropical eosinophilia should be considered first in the diagnosis. If the typical symptomatology is present, the diagnosis is beyond doubt. Even if it is not present, a very high E.S.R. and positive Wassermann and/or Kahn reactions justify such a diagnosis and the consequent therapeutic trial with arsenic. An initial exacerbation with subsequent rapid improvement, clinically after arsenical treatment, will practically settle the diagnosis."

It would now seem desirable to ascertain if all cases of Löffler's syndrome regardless of the etiology respond to organic arsenical therapy in the manner just described. It would also be interesting to determine the effect of such therapy on the course of human as well as experimental clonorchiasis. It cannot be claimed from the extremely limited data presented here that organic arsenicals are effective clonorchicidal agents. The effect may only be hematologic and non-specific or fortuitous.

SUMMARY

A case of clonorchiasis with marked eosinophilia in the peripheral blood and bone marrow and bilateral pulmonary infiltrations is presented. The similarity and possible relation of this condition, Löffler's syndrome and tropical eosinophilia (eosinophilic lung) are discussed. It is predicted that clonorchiasis will be a problem in many of the returning military personnel from China, Japan and Korea and that this condition will have to be considered in patients presenting marked eosinophilia.

REFERENCES

1. BERCOVITZ, Z. Clinical studies on human infestations with the liver fluke (*Clonorchis sinensis*). *Am. J. Trop. Med.*, 11: 43, 1931.
2. FAUST, E. C. and KHAW, O. K. Studies on *Clonorchis sinensis*. *Am. J. Hyg.* Monograph series No. 8, 1927.
3. FAUST, E. C. Human Helminthology, 2nd ed., p. 222. Philadelphia, 1939. Lea and Febiger.
4. HOEPLI, R. Histological changes in the liver of sixty-six Chinese infected with *Clonorchis sinensis*. *Chinese M. J.*, 47: 1125, 1933.

5. OTTO, J. H. Clinical, pathophysiological and therapeutical aspects of human clonorchiasis. *Far East. Trop. Med., Tr. Ninth Cong.*, 1: 543, 1934.
6. ITO, K. Blood features of the rabbit experimental clonorchiasis. In *Jap. M. World*, 7: 275, 1927.
7. YOUNG, S. The changes in the haematopoietic organs and the blood picture in experimental liver-distomiasis. *Jap. J. Exper. Med.*, 9: 47, 1931.
8. TOMI, G. On the blood feature in a case having infection from *Opisthorchis sinensis*. *J. Okayama M. Soc.*, 376: 1921. In *Jap. M. World*, 1: 5, 25, 1921.
9. TOYAMA, G. Ueber den Blutbefund bei Leberdistomiasis. *Okayama Igakkai-Zasshi*, 384, 1921. In *Jap. J. M. Sc.*, 1: 59, 1922.
10. LÖFFLER, W. Zur Differential-diagnose der Lungeninfiltrierungen; über flüchtige Succedan-Infiltrate (mit Eosinophilie). *Beitr. z. Klin. d. Tuberk.*, 79: 368, 1932.
11. LÖFFLER, W. Die flüchtigen Lungeninfiltrate mit Eosinophilie. *Schweiz. med. Wchnschr.*, 66: 1069, 1936.
12. WRIGHT, D. O. and GOLD, E. M. Löffler's syndrome associated with creeping eruption (cutaneous helminthiasis). *Arch. Int. Med.*, 78: 303, 1946.
13. HERBUT, P. A. and KINSEY, F. R. Transitory pulmonary infiltrations (Loeffler's syndrome) in rabbits. *Arch. Path.*, 41: 489, 1946.
14. FRIMODT-MÖLLER, C. and BARTON, R. M. A pseudo-tuberculous condition associated with eosinophilia. *Indian M. Gaz.*, 75: 607, 1940.
15. WEINGARTEN, R. J. Tropical eosinophilia. *Lancet*, 1: 103, 1943.
16. SIMEONS, A. T. W. Pseudo-tuberculosis of lungs with eosinophilia. *Indian M. Gaz.*, 78: 271, 1943.
17. TREU, R. Pseudo-tuberculosis of the lungs with eosinophilia. *Indian M. Gaz.*, 78: 70, 1943.
18. HODES, P. J. and WOOD, F. C. Eosinophilic lung (tropical eosinophilia). *Am. J. M. Sc.*, 210: 288, 1945.
19. JHATAKIA, K. U. Observations on eosinophilic lung. *Indian M. Gaz.*, 81: 179, 1946.
20. D'ABRERA, V. ST. E. and STORK, K. G. Serological reactions in tropical eosinophilia. *Indian M. Gaz.*, 81: 282, 1946.
21. MENON, C. K. Tropical eosinophilia: some further observations. *Indian M. Gaz.*, 81: 70, 1946.
22. VISWANATHAN, R. Pulmonary eosinophilosis, *Indian M. Gaz.*, 80: 392, 1945.
23. CARTER, H. F. and D'ABRERA, V. ST. E. Mites (acarina). A probable factor in the aetiology of spasmodic bronchitis and asthma associated with high eosinophilia, *Tr. Roy. Soc. Trop. Med. & Hyg.*, 39: 373, 1946.
24. D'ABRERA, V. ST. E. Further observations on cases of asthma and bronchitis associated with high eosinophilia and with mites in the sputum. *Indian M. Gaz.*, 81: 414, 1946.
25. VAN DER SAR, A. Pulmonary acariasis, its relationship to the eosinophil lung and Löffler's syndrome. *Am. Rev. Tuberc.*, 53: 440, 1946.
26. DE LANGEN, C. D. Anguilliosis en het ziektebeeld van de idiopathische hyperosinophilie. *Geneesk. tijdschr. v. Nederl.-Indië*, 67: 973, 1928.
27. MEYERS, F. M. and KOUWENAAR, W. Over hyper-eosinophilie en over een merkwaardige vorm van filariasis. *Geneesk. tijdschr. v. Nederl.-Indië*, 79: 853, 1939.

Co-existent Chronic Glanders and Multiple Cystic Osseous Tuberculosis Treated with Streptomycin*

C. RAY WOMACK, M.D. and E. BUIST WELLS, M.D.

Nashville, Tennessee

Boston Massachusetts

THE co-existence of glanders and osseous tuberculosis is a rare occurrence. This is a report of a recently observed case in which both infections were present. The unusual character of the case and the treatment with streptomycin† warrant this report.

Glanders in man is an uncommon occupational disease of protean nature. Preventive measures have almost eradicated the disease in the equine species and consequently in man.⁷

In 1906 Robins⁹ analyzed 156 cases of human glanders collected from the literature. Stewart¹⁰ in 1904, Gaiger³ in 1913, Bernstein and Carling¹ in 1909, Burgess² in 1936, Mendelson⁸ in 1936, Herold and Erikson⁴ in 1938 and Howe and Miller⁵ in 1947 contributed to our knowledge of the human disease.

Human infection with the causative micro-organism, *Malleomyces mallei*, presents a varied clinical picture characterized by the formation of granulomatous lesions in the skin and subcutaneous tissues, chronic ulceration of mucous membranes with profuse discharges from the nose, mouth and throat, or pulmonic and pleuritic manifestations. Any one or all of these sites may be involved and the picture may be complicated by metastatic hematogenous spread to meninges, bones, joints and abdominal viscera. The disease may run an acute, fulminating, fatal course or it may persist chronically with remissions and exacerbations

for as long as fifteen years. A few patients recover spontaneously; the majority die. The clinical picture is greatly complicated by the concurrence of osseous tuberculosis as was present in one of the cases cited by Robins.⁹

CASE REPORT

A. E. R., a blacksmith, age fifty-four, was admitted to the Vanderbilt University Hospital, December 10, 1945, complaining of cutaneous abscesses. For about a year before the present illness he had repeatedly shod mules suffering from chronically draining ulcers of the legs and had frequently contacted pus from these lesions. The present illness began six years before admission when he developed a small ulcer on the left forearm accompanied by slight malaise and fever. A month later tender, generalized adenopathy developed. A cervical node was excised and examined. The histologic report was "acute and chronic inflammatory tissue." The surgical wound rapidly broke down and at the site an indolent ulcer developed which drained purulent material for a period of three to four months; eventually it healed. However, intermittently during the subsequent years tender nodules involving the skin of the neck, chest and extremities developed. These would spontaneously rupture and drain thick, yellow pus and were accompanied often by fever and occasionally by shaking chills. During the intervening periods he apparently felt well.

A year before admission he noted swelling, redness and tenderness of the scrotum which persisted until his admission to the hospital. Four months later pain and deafness developed

* From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

† The streptomycin used was furnished by Dr. Chester S. Keefer, Boston, Mass.

in the right ear in association with a foul, purulent discharge. Both drainage and deafness persisted. Two weeks before admission paralysis of the right side of the face occurred.

The past history was not remarkable. Nasal "catarrh" had been present since childhood and nasal secretions were somewhat more profuse during the present illness. During the six years prior to admission he gradually lost 30 pounds in weight.

Upon admission to the hospital the temperature was 98.6°F., pulse rate 70, respiratory rate 20, and blood pressure 125/85. He was well developed but very poorly nourished and appeared chronically ill. There were depressed, stellate scars about the neck, upper chest, hands and legs. On the left forearm near the wrist were two swollen, encrusted lesions with surrounding erythema. From these thick, creamy pus could be expressed. There was generalized, soft swelling about the left wrist. The right wrist and metacarpophalangeal joints were ankylosed. A firm, slightly fluctuant nodule was present on the dorsum of the right hand. The lymph nodes were generally enlarged and firm but were not tender. A peripheral type of right facial paralysis was present. There was a thin, foul, purulent discharge in the right auditory canal and the drum was perforated, thick and white. He was almost deaf in this ear; the Weber test showed no reference of sound, and Rinne's test revealed bone conduction to be greater than air conduction on the right. The nasal mucosa was raw and inflamed and there was a slight mucopurulent discharge. The chest was symmetrical and thin. A harsh friction rub was heard at the base of the right lung posteriorly and signs of a small, right-sided pleural effusion were present. The heart appeared to be normal. The liver was palpable two fingerbreadths below the right costal margin; it was smooth and not tender. The spleen was not felt. The scrotum was enlarged to about twice the normal size and was tender, red, brawny and thickened. The scrotal wall did not pit upon pressure. It transmitted light and appeared to contain fluid. The reflexes were not remarkable.

Laboratory data included a red blood count of 4,000,000 with a hemoglobin value of 11.0 Gm. The white blood count was 7,450 with a normal differential count. The sedimentation rate was 34 mm. per hour (Wintrobe). The Kahn test and the Wassermann reaction of the blood were negative. Urine and stool examina-

tions were normal. The blood non-protein nitrogen level and phenolsulfonphthalein excretion were within normal limits. The total serum protein was 6.4 Gm. per cent (2.9 Gm. albumin and 3.5 Gm. globulin; A/G ratio, 0.8). The blood calcium, phosphorus, alkaline phosphatase and acid phosphatase values were normal. A Congo red test gave normal results. The bromsulfalein and cephalin-cholesterol flocculation tests of liver function were normal. The cerebrospinal fluid was sterile and normal in all other respects. Repeated blood cultures yielded no growth.

An x-ray of the chest revealed thickened apical pleura bilaterally and both right interlobar fissures were visible. A small pleural effusion was present on the right. The heart was not enlarged. X-rays of the skeleton showed widespread bone atrophy and several destructive lesions. There was an area of bone destruction 3 cm. in diameter in the region of the right mastoid. Areas of bone destruction of variable size and shape were present bilaterally in the radiuses, ulnas, metacarpals, phalanges, taluses and in the medial malleoli of the tibiae. A lesion measuring 5 by 1 cm. in the distal end of the left femur showed elevation of the overlying periosteum and some changes suggestive of bone production.

Attempted aspirations of the swollen left wrist and of the nodular lesion on the dorsum of the right hand were unsuccessful. A right thoracentesis yielded 40 cc. of amber fluid which clotted upon standing. It contained 1,500 red cells and 560 leukocytes per cu. mm.; 68 per cent of the latter were polymorphonuclear cells. The specific gravity of the fluid was 1.025, and the protein content 6.25 Gm. per cent. Gram-stained smears of this fluid showed no organisms and cultures produced no growth. No acid-fast organisms were demonstrated by smear or guinea pig inoculation.

Stained smears of pus from the right ear and the ulcer on the left wrist revealed gram-positive cocci in clumps and chains and numerous, small, slender, lightly stained gram-negative bacilli which were preponderantly extracellular. They presented the typical appearance of *M. mallei*. Curved and slightly clubbed forms were numerous and they presented a beaded appearance. The microscopic picture was strikingly similar in morphology and grouping to tubercle bacilli but they were not acid-fast.

Cultures of the pus on blood agar yielded

many colonies which were readily identified as *Staphylococcus aureus* and beta hemolytic streptococci. Among them, and in marked excess at twenty-four hours, were numerous, small, "dew-drop," translucent colonies. These were composed of organisms identical morphologically and in their staining reaction with the gram-negative bacilli observed in direct smears. Isolated in pure culture, this micro-organism showed the typical growth behavior of *M. mallei* except that attempts to grow the organism on potato to demonstrate the typical colony growth and pigment production were unsuccessful. These bacteria were insensitive to penicillin *in vitro* but growth was completely inhibited by 3 micrograms of streptomycin per cc. of culture medium.

Agglutination reactions performed with the patient's serum and the bacilli were positive in dilution up to 1:1,280. The patient's serum agglutinated a known strain of *M. mallei*, obtained from the American Type Culture Collection, in dilutions up to 1:256.

Although the above data were suggestive that the organism was a strain of the glanders bacillus, conclusive evidence was not obtained until cross-agglutination studies were performed. Antisera were prepared by immunizing rabbits with the patient's organism and with the known type strain of *M. mallei*. Serum immune to the patient's organism agglutinated the homologous strain in dilutions up to 1:640 and *M. mallei* up to 1:160. Serum immune to the type-strain agglutinated the homologous organism in dilutions up to 1:160 and the type-strain in dilutions up to 1:640.

It is of interest that specimens of the patient's serum were sent to the Bureau of Animal Industry, U. S. Department of Agriculture, and to the Army Veterinary School, Washington, D. C., for complement fixation tests against *M. mallei*. The results were negative in each instance.

Diagnostic intradermal tests with commercial mallein were performed during his several admissions after the above serologic studies were obtained. The amount employed in testing ranged from 0.1 cc. of 1:100,000 dilution on the first admission to 0.1 cc. of the undiluted antigen. In this instance a zone of tender, red swelling 3 by 5 cm. in diameter appeared within three hours. It was unaccompanied by any constitutional reaction and disappeared within twenty-four hours. This result was interpreted as being non-specific.

Guinea pigs inoculated intraperitoneally with the entire forty-eight-hour growth of the bacillus on a blood agar slant did not succumb to infection as expected, nor could the micro-organism be recovered by culture from the peritoneum seventy-two hours after injection. This was presumed to be due to the organism's low virulence. Guinea pigs inoculated subcutaneously with pus obtained directly from the ear and skin ulcers did not show evidence of acute infection nor did the so-called Strauss reaction develop.

Acid-fast bacilli were not demonstrated in smears of pus from the ear or from the draining cutaneous ulcers. However, injection of this material into guinea pigs, as mentioned above, resulted in the development of tuberculosis. Acid-fast bacilli typical of *Mycobacterium tuberculosis* were readily demonstrated in smears from the lesions produced. Fluid aspirated from the bone cyst in the right radius was sterile on routine culture but induced tuberculosis when injected into guinea pigs. Pus aspirated from a subcutaneous abscess which appeared on the dorsum of the right hand shortly before the patient's second admission contained acid-fast organisms which proved to be tubercle bacilli upon guinea pig inoculation. An intradermal test with 0.1 mg. of old tuberculin produced a positive reaction in forty-eight hours.

Repeated sputum examinations were negative for tubercle bacilli. During subsequent admissions and during the follow-up studies material from the ear and the draining lesions was examined repeatedly for tubercle bacilli but none were demonstrated.

Penicillin, 20,000 units intramuscularly every three hours, was administered for ten days. Within about four days the right facial paralysis had entirely disappeared and there was great improvement in the cutaneous lesions. The erythema surrounding the lesions subsided considerably and there was great reduction in the purulent drainage. Cultures from the ear and left wrist after completion of the course of penicillin yielded neither staphylococci nor streptococci. A pure culture of *M. mallei* was obtained.

Upon completion of the course of penicillin treatment streptomycin hydrochloride, 0.2 Gm. intramuscularly five times daily, was started. Within twenty-four hours severe swelling and pain developed in the left wrist, accompanied

by aching in the knees, ankles and elbows. On the fourth day of streptomycin treatment the temperature rose to 100.2°F. The patient experienced severe arthralgia and pain on movement of all the joints. The right mastoid region became tender. The fever, arthralgia and mastoid pain subsided the following day and he remained afebrile thereafter. The inguinal and femoral lymph nodes decreased in size. Six days after the initiation of streptomycin treatment the glanders bacillus could not be cultured from the ear or skin lesions. The patient was discharged on his thirty-third hospital day having received a total of 13.0 Gm. of streptomycin. All skin lesions were encrusted, had ceased draining and appeared to be healing. The ear continued to drain but drainage was greatly decreased.

He was readmitted on February 12, 1946, for re-evaluation. During the interval he had felt well and had gained 16 pounds in weight. The right ear had continued to drain following his discharge from the hospital but no cutaneous abscesses had developed until four days before admission when one appeared on the dorsum of the right hand. Pus aspirated from the lesion contained *M. tuberculosis*. A sinus tract later formed at this site and discharged sporadically. During this admission it was impossible to culture the glanders bacillus from any site which previously had yielded it nor could it be demonstrated on direct smear. X-ray examinations of the chest and the bones revealed no significant changes. He was discharged after ten days.

During the following nine days pain and redness involving the right ankle and generalized arthralgia developed accompanied by malaise and chilly sensations. A right inguinal node had become swollen and drained spontaneously and intermittently. He was readmitted to the hospital on March 2nd for a second course of streptomycin. Attempts to demonstrate the glanders bacillus in material from the ear, the draining sinuses and the healing cutaneous ulcers again failed; neither could tubercle bacilli be found. Streptomycin hydrochloride in the previous dosage was again administered, with total dosage of 10.0 Gm. A transient exacerbation of the arthritis and arthralgia again occurred although the reaction was milder than the previous one and was unaccompanied by fever. The course in the hospital was entirely afebrile and uneventful and he was discharged after thirteen days.

Follow-up studies were obtained at approximately two-month intervals for a period of six months. During this time he improved but was unable to assume full activity. He remained afebrile and gained weight slowly. The ulcerated area on the left wrist, the sinus tract on the dorsum of the right hand, the right ear and the inguinal sinus drained occasionally. Neither organism previously isolated could be demonstrated in these discharges. Roentgenograms of the involved bones showed no remarkable change except for the right mastoid in which there was some evidence of healing.

In December, 1946, the patient was seen at another hospital complaining of right-sided pleuritic pain, dyspnea, fever and occasional chills. Two thoracenteses were performed on the right yielding a total of 1,500 cc. of amber fluid which was sterile on culture. Examinations for tubercle bacilli, including cultures, were negative. The patient left the hospital improved and was readmitted in March, 1947, in a critical condition, very dyspneic and emaciated. Thoracentesis yielded only 500 cc. of amber fluid. A chest x-ray contributed no significant information. One day after admission the patient suddenly complained of excruciating chest pain and rapidly expired. Permission for necropsy was not obtained. Clinically, it was believed that death was due to coronary occlusion or possibly pulmonary embolism. During both admissions it was the opinion of his physician that no significant change had developed in the condition of the sites showing intermittent drainage.

COMMENT

There seems to be little doubt that this patient had both chronic glanders and tuberculosis of bone, the latter corresponding to the osteitis tuberculosa multiplex cystica of Jüngling.⁶ The tubercle bacillus was recovered from the bone cysts, subcutaneous abscesses and material from draining sinuses overlying the bone lesions. Gram-negative bacilli morphologically resembling the glanders bacillus were isolated from the right ear and from an ulcer on the left wrist, sites which overlay destructive osseous lesions. Cross agglutinations indicated these organisms to be identical with a type culture of *M. mallei*.

The glanders bacillus was found to be insensitive to penicillin *in vitro* but was moderately sensitive to streptomycin. Penicillin caused partial healing of the skin lesions, apparently by eliminating pyogenic cocci, but had no effect on the glanders bacilli. Streptomycin effected further striking improvement in the skin ulcers and draining sinuses. Following streptomycin therapy *M. mallei* could not be demonstrated in the lesions again. There was no significant change in the x-ray appearance of the bone lesions. It seems probable that streptomycin cured the patient of glanders but had little effect upon the tuberculosis, unless the tendency toward healing of the sinus tracts overlying bone lesions might be considered such an effect. It should be emphasized that due to a limited supply the dosage of streptomycin was small and whether or not larger doses would have had a more favorable effect upon the tuberculosis cannot be stated. The efficacy of sulfadiazine was not determined in this patient. Howe and Miller⁵ found this drug effective both in experimental animal infections with *M. mallei* and in their six acute cases.

The patient's transient reaction of fever, arthralgia and exacerbation of pain in the lesions, which occurred at the onset of both courses of streptomycin, was of great interest. Early lots of streptomycin occasionally caused reactions consisting of fever, arthralgia and headache, supposedly due to histamine-like substances in the less completely purified drug. Such reactions have been most infrequent recently. The fact that a similar reaction occurred in this patient on two occasions, with different lots of streptomycin, and that it was an exacerbation of pre-existing symptoms seem to indicate a reaction to bacterial protein similar to the Herxheimer reaction seen in syphilis under treatment.

The mallein test and the complement fixation test for glanders were repeatedly

negative. These results do not invalidate the diagnosis of glanders. A number of Robins'⁹ cases had negative mallein tests. Two of the six cases reported by Howe and Miller⁵ had negative complement fixation tests and one had a negative mallein test.

The patient's scrotal inflammation was interesting and the similarity to the Strauss reaction in guinea pigs was striking. No attempts were made to demonstrate the presence of the glanders bacillus in this area.

SUMMARY

1. A case is presented in which chronic glanders and cystic tuberculosis of bone co-existed. The causative organisms of both diseases were isolated and identified.*

2. Penicillin therapy was ineffective. Treatment with streptomycin seemed to be curative for glanders but in the dosage used had little or no effect upon the tuberculosis of bone.

REFERENCES

1. BERNSTEIN, J. M. and CARLING, E. R. Observations on human glanders. *Brit. M. J.*, 1: 319-325, 1909.
2. BURGESS, J. F. Chronic glanders. *Canad. M. A. J.*, 34: 258-262, 1936.
3. GAIGER, S. H. Glanders in man. *J. Comp. Path. & Therap.*, 26: 223-236, 1913.
4. HEROLD, A. A. and ERIKSON, C. Human glanders: case report. *South. M. J.*, 31: 1022, 1938.
5. HOWE, C. and MILLER, W. R. Human glanders: a report of six cases. *Ann. Int. Med.*, 26: 93-115, 1947.
6. JÜNGLING, O. Ostitis-tuberculosis multiplex cystica (eine eigenartige Form der Knochentuberkulose). *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 27: 375-383, 1919-1921.
7. MCGILVRAY, C. D. The transmission of glanders from horse to man. *Canad. J. Pub. Health*, 35: 268-275, 1944.
8. MENDELSON, R. W. Glanders. *Ann. Int. Med.*, 10: 43-48, 1936.
9. ROBINS, G. D. A study of chronic glanders in man with report of a case. *Stud. Roy. Victoria Hosp., Montreal*, 2: 1, 1906.
10. STEWART, J. C. Pyemic glanders in the human subject. *Ann. Surg.*, 40: 109-113, 1904.

* We are indebted to Dr. Roy C. Avery and Dr. G. John Buddingh of the Department of Pathology and Bacteriology, Vanderbilt University School of Medicine, for their assistance in isolating and identifying the micro-organisms from this case.

Hemochromatosis*

Cardiac Failure Associated with Extensive Hemosiderosis of the Myocardium

HOWARD L. HORNS, M.D.

Minneapolis, Minnesota

ALTHOUGH the occurrence of extensive hemosiderosis of the myocardium in cases of hemochromatosis is a frequent autopsy finding, associated disturbances of cardiac function have rarely been noted. For this reason the present case is of interest.

CASE REPORT

The patient, a fifty-four year old male, entered the University of Minnesota Hospital on the otolaryngology service February 10, 1945, with complaints of bilateral hearing loss and left-sided facial paralysis of eight months' duration. He had had chronic otitis media since the age of two following scarlet fever, and in June, 1944 he had suffered acute bilateral ear infections followed by complete hearing loss. Two weeks later complete left facial paralysis suddenly appeared. In July of the same year an increase in thirst, appetite and urine output was noted and at the same time a brownish pigmentation of the hands, arms and groins was observed for the first time. The diabetes was controlled with 35 to 40 units of protamine insulin daily.

Three years before admission the patient had a series of attacks of transient, severe precordial pain radiating into the neck. The attacks were not related to exertion and were untreated; after a few weeks they ceased and did not recur. However, during the succeeding months he noted mild exertional dyspnea and orthopnea requiring two pillows for comfortable slumber. For one month prior to admission slight ankle edema which disappeared with rest was present. The past history was otherwise non-contributory. By occupation he had been a farmer and day laborer. His alcohol consumption was limited to an occasional glass of beer. There were no other

instances of diabetes or of excessive pigmentation in members of his family. He was married and had two children.

Upon physical examination the patient was found to be a well developed, middle-aged male in no acute distress. The skin was diffusely pigmented with a grayish brown color marked on the face, hands, forearms, linea alba, intercrural regions and scrotum.

Except for ectropion of the left lower lid the eyes were normal. There was paralysis of both upper and lower facial muscles on the left side and the tympanic membranes of both ears were completely destroyed. No other abnormalities of the head and neck were noted.

The chest was of normal contour and the lung fields were clear. The heart was slightly enlarged, a soft systolic murmur was audible over the entire precordium but was not transmitted to the axilla. The pulse rate was 80 with a regular rhythm; blood pressure ranged from 106/60 to 120/70 on a series of determinations.

The liver was found to extend 9 cm. below the costal margin in the right mid-clavicular line and the spleen was palpable 3 cm. below the costal margin. Both were described as being smooth, firm and non-tender. Except for the scar of an old hernial repair the remainder of the abdomen was normal.

There was slight, but definite pitting edema of the feet and ankles; the reflexes were physiologic.

Laboratory examination revealed the following representative findings: Urine: specific gravity, 1.010-1.031; pH, 5-7; glucose, 0-4; erythrocytes and leukocytes consistently absent; occasional casts. Blood: hemoglobin, 13-14.4 Gm.; red cells, 5,040,000; leukocytes, 4800-7450, with a normal differential count. Blood chemistries: blood urea nitrogen, 11 mg. per cent; blood sugar, 67-327 mg. per cent; CO₂

* From the Department of Internal Medicine, University of Minnesota Medical School and University Hospital, Minneapolis, Minn.

combining power, 69 volumes per cent; blood chlorides, 596 mg. per cent; blood cholesterol, 148–189 mg. per cent. Total plasma proteins were 6.2 Gm. per cent, with 3.6 Gm. of albumin and 2.6 Gm. of globulin. Of the liver function studies the total serum bilirubin was 1.2 mg. per cent with 0.4 mg. per cent in the 1-minute prompt reacting fraction; the cephalin cholesterol test showed 2+ and 3+ flocculation at twenty-four and forty-eight hours; there was 80 per cent of normal excretion of hippuric acid and the serum alkaline phosphatase value was 16 Bodansky units. There was 10 per cent retention of phenolsulfonphthalein dye and the urine urobilinogen was consistently elevated to 12 to 15 mg. daily. The arm to lung circulation time was 12 seconds and that for arm to tongue 19 seconds; a venous pressure of 7 cm. of citrate solution was recorded in the antecubital vein.

Chest x-ray was interpreted as showing a slightly enlarged heart of the left ventricular type. Electrocardiogram revealed borderline QRS voltage, isoelectric T₁ and questionably diphasic T₂.

During the course in the hospital a radical endaural mastoidectomy was done on the left side in the hope of relieving the facial paralysis. This was of no avail and lid suture was carried out to prevent injury of the left cornea. The clinical diagnosis of hemochromatosis was confirmed by liver biopsy. The diabetes was controlled without difficulty and the ankle edema disappeared with rest. He was discharged on March 17th.

During the succeeding two months the diabetes was controlled without difficulty. However, the patient was incapacitated by progressively increasing edema of the lower extremities, with the ultimate development of scrotal edema and ascites which necessitated re-admission to the hospital on May 14th. At this time the physical findings differed from those of the previous admission in the presence of massive edema of the legs and scrotum, shifting dullness in the flanks and scattered rales in the lung bases posteriorly.

The laboratory findings were essentially the same as before. The total serum protein was 6.5 Gm. per cent with 3.7 Gm. of albumin. The venous pressure was markedly elevated, being 18.5 cm. of citrate; arm to tongue and arm to lung circulation times were 13 and 29 seconds, respectively. The electrocardiogram at this

time showed much lower QRS voltage in all leads and diphasic T₁ and T₂.

The patient was treated with digitalis, low salt diet and mercurial diuretics; however, his edema progressively increased while at bed rest; dyspnea, orthopnea and mild cyanosis appeared. Terminally he developed convulsions which were not related to hypoglycemia; he then became comatose and expired on June 12th.

At autopsy the body was that of a well developed male with pigmentation and marked edema as previously noted. The abdomen was protuberant with ascitic fluid. The pleural cavities each contained 600 cc. of clear yellow fluid. The right lung weighed 540 Gm., the left 460 Gm.; bronchi and pulmonary vessels appeared normal. The heart weighed 440 Gm., the ventricular walls were hypertrophied and there was some dilatation of the left ventricle. The valves were entirely normal. The muscle was quite brown and flabby; on cut section there was no evidence of infarction or fibrosis. The coronary arteries showed no evidence of arteriosclerosis; they were soft and easily distensible throughout. The liver weighed 1,940 Gm. and was finally nodular and pigmented. The spleen weighed 800 Gm. and was firm and dark red in color on section. The pancreas was deeply pigmented; the adrenals appeared normal. The right and left kidneys weighed 200 and 220 Gm., respectively; no abnormalities were noted. The aorta was normal.

Microscopically, the lungs contained many heart failure cells and exhibited some areas of atelectasis. The muscle fibers of the heart were pale-staining. There was fragmentation in some areas, with an increase in the spaces between the fibers. Cross striations were only faintly present or were absent. The muscle fibers were heavily infiltrated with pigment which stained blue with ferrocyanide. In some areas the muscle substance appeared to be almost entirely replaced. The other organs showed the ordinary findings of hemochromatosis.

COMMENTS

Hemosiderin deposition of severe degree within the muscle fibers of the myocardium is a common autopsy finding in cases of hemochromatosis. Sheldon¹ in his extensive review reported such deposits present in 90 per cent of the cases which included ade-

quate microscopic data to permit evaluation. Althausen and Kerr² noted this finding in thirty-three of forty cases they reviewed. Despite this frequency of demonstrable involvement, cardiac symptoms have not been a conspicuous feature in the clinical picture of hemochromatosis. Sheldon¹ notes that there have been some instances of heart failure and in classifying his cases as to cause of death he groups 10 per cent under "various intercurrent conditions and myocardial failure." He fails to state whether any of the ordinary causes of heart failure were present in these cases. However, he apparently did not consider the cases remarkable so presumably the heart failure was considered due to the ordinary causes.

In French literature^{3,4} heart failure is noted to be a regular occurrence in what is perhaps a special group of cases of hemochromatosis. A symptom complex is described under the name of the endocrino-hepato-cardiac syndrome which is characterized by the following features: occurrence in a younger age group; multiple involvement of the endocrine glands, particularly the testes which are atrophic; infantilism and death from cardiac decompensation. Because myocardial infiltration could not be demonstrated in the autopsy material of some of these cases, most of these authors thought that the heart failure was not explained on a basis of myocardial damage by hemosiderin deposits but rather was due to a generalized metabolic disorder of uncertain nature.

Recent English and American literature contains reports⁵⁻⁸ describing a total of nine cases of hemochromatosis in which cardiac symptoms have been prominent. Of these subjects six died and autopsies have been performed. In all of them extensive hemosiderin deposits were present

in the myocardium; one,⁶ however, had coronary disease in addition. In the others the coronary arteries were normal, no valvular lesions were present and there were no histories of hypertension. It is of interest that in three of these cases severe precordial pain with radiation was such a prominent symptom that in two a diagnosis of coronary occlusion was made and later disproved at autopsy. The most common electrocardiographic change has been low voltage. There was complete heart block in two and auricular fibrillation in two others.

In the present case it is believed that with the exclusion of valvular lesions, coronary disease and hypertension as causes of heart failure the cardiac symptoms must be attributed to myocardial degeneration associated with extensive hemosiderin deposits within the heart muscle.

REFERENCES

1. SHELDON, J. H. *Haemochromatosis*. London, 1935. Oxford University Press.
2. KERR, W. J. and ALTHAUSEN, T. L. Hemochromatosis. Report of three cases with endocrine disturbances and notes on previously reported case. Discussion of etiology. *Endocrinology*, 17: 621, 1933.
3. BEZANCON, F., DEGENNES, L., DELARUE, J. and OUMANSKY, V. Cirrhose pigmentaire avec infantilisme, insuffisance cardiaque et aplasies endocriniennes multiples. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 48: 967, 1932.
4. DEGENNES, L. and GERMAIN, A. Sur deux nouveaux cas de cirrhose pigmentaire avec infantilisme et défaillance cardiaque (syndrome endocrino-hepato-cardiaque), *Bull. et mém. Soc. méd. d. hôp. de Paris*, 56: 665, 1940.
5. PETIT, DONALD W. Hemochromatosis with complete heart block. *Am. Heart J.*, 29: 253, 1945.
6. BLUMER, G. and NESBIT, R. R. Case of hemochromatosis with degeneration of heart muscle and death from congestive heart failure. *New England J. Med.*, 218: 295, 1938.
7. MURRAY, LYON, R. M. Haemochromatosis: report on 3 cases. *Brit. M. J.*, 1: 1297, 1936.
8. MALING, T. C. and RILEY, G. Haemochromatosis: report on case. *New Zealand M. J.*, 36: 314, 1937.

Editorial

Problems of Hepatic Disease

THE great pandemic of hepatitis involving millions of persons during and following World War II is probably the greatest factor in stimulating the current intense interest in disorders of the liver. Clinicians are being confronted more frequently than ever with baffling problems in the differentiation of this disease from other conditions causing jaundice, especially those requiring surgical intervention, as well as in the recognition of progressive subclinical inflammatory processes and of residual disability which require proper management.

Similar problems are raised by the increasing exposure of large numbers of our population to substances which are potentially injurious to the liver, such as organic solvents, industrial fumes, insecticides and some of the newer medications. It would be truly a great advance if the toxic effects of these agents could be evaluated before irreparable damage has taken place.

There is the challenge, too, presented by that formidable group of mortals who depend somewhat too heavily upon ethanolic solace. The hepatotoxic effects of alcohol vary markedly in different subjects and it is deplorable that the protruding abdomens and dilated veins of the susceptible few force the physician into warning generalities for want of methods to evaluate the tolerance factors of the individual.

Problems such as these have aroused a wholesome spirit of inquiry as to the significance and reliability of the various function tests that may be applied to the

detection of impaired hepatic physiology. Current medical literature abounds in conflicting reports by well trained observers which serve but to emphasize the intrinsic complexities of the problem. Agreement is general, however, that no single test has yet been devised which can be used as an infallible index of the nature or extent of hepatic derangement. The limitations of liver function tests are due in part to the fact that the same disease entity, such as hepatitis or neoplasm, may affect sometimes one and sometimes another portion of the hepatic unit but chiefly because the activities upon which our tests are based are still beyond our mechanistic comprehension.

In a sense, the liver is not a single organ and for the sake of clarification may be regarded in the light of at least four aspects:

First, it stands as a vascular maze through which the portal blood must pass before it joins the systemic circulation. Only recently have methods been devised to estimate the total blood flow through the liver in health and disease, but maldistribution of blood within the organ due to sinusoidal dilatation or constriction, swelling of parenchymal cells, compression due to intrahepatic tension, inflammation or scarring of the portal areas, passive congestion, etc., must be recognized chiefly by clinical inference since no tests are yet available to evaluate such circulatory variables. These may exert a profound effect on the function and even viability of the hepatic tissues.

Second, about one-third of the entire hepatic mass is composed of Kupffer cells,

reticulum and other tissues¹ stemming from the mesenchyme. Thus it stands second only to bone marrow as a reticulo-endothelial organ and like the spleen, lymph nodes, etc., often is affected by diseases involving this important system.

Third, it is an excretory organ. Bile, composed of substances removed from the blood by hepatic activity or synthesized by the parenchymal cells, takes origin within the biliary capillaries which are in essence spaces among the clusters of polygonal cells. Only after these small tracts emerge from the lobule and coalesce to form delicate ducts do they constitute a separate anatomic unit, namely, the biliary tree. Widespread lesions in the periphery of the hepatic lobules, as is occasionally observed in hepatitis and infectious mononucleosis, may cause disruption of these friable structures with the production of jaundice without necessarily impairing the general functions of the liver.

Fourth, and most difficult of all to evaluate by exact measurements, are the intricate metabolic activities of the parenchymal cells which regulate the disposal of almost all foodstuffs and their by-products according to the nutritive requirements of the entire organism. These activities are usually ascribed to integrated enzyme systems but the mechanisms by which balances are maintained are not known. Certain determinations, for example the cholesterol-cholesterol ester content of the serum or the serum albumin, empirically reflect two metabolic equilibria maintained by the liver which are altered in characteristic patterns in certain diseases. Most of the routine metabolic tests for liver function are relatively insensitive and when modifications are introduced to overcome these disadvantages intercurrent variables not pertaining directly to the liver may lead to serious errors.

The clinical appraisal of liver disorders depends upon careful evaluation of the aforementioned factors, such as the extent of portal hypertension, the degree of biliary obstruction, the type of metabolic derange-

ment and the activity of the disease process. It is obvious that the laboratory alone is not yet qualified to give answer to all these considerations; and even when our most reliable tests are properly selected and skillfully integrated with all the clinical features of the disease, an accuracy of diagnosis exceeding 90 per cent can seldom be attained.

Uncertainties and difference of opinion are also widespread in the therapeutic field, especially in regard to dietary management. It has been demonstrated by numerous clinical and laboratory studies that diets low in protein and in lipotropic agents such as choline lead to degenerative changes within the hepatic lobules or to fatty infiltrations which, in turn, render the cells less viable and more susceptible to noxious agents, anoxia and other intercurrent mishaps. The importance of these observations is enhanced by the demonstration of Patek and his associates that the downward trend in a fair proportion of cases of Laennec's cirrhosis can be arrested and actually reversed by a high protein diet rich in vitamin supplements. This significant contribution has led to widely held misconceptions that diet is all-important in the management of hepatic disease in general. Furthermore, the observations of toxicologists and experimental nutritionists on the protective action on the liver of certain accessory factors in the diet of malnourished animals or those exposed to toxic agents has given rise to widespread clinical employment of such substances as methionine, choline, crude liver, vitamin K, tocopherol, pyridoxine, human albumin and protein hydrolysates, in a haphazard array of hepatopathies ranging from acute yellow atrophy to cases of palpable Riedel's lobes. Low fat, high protein diets are also being routinely enforced irrespective of the underlying disorder, a practice which often causes no improvement and may actually add to the emaciation and debilitation of the patient. The experience of many observers indicates that the therapeutic effectiveness of diet in hepatic disease bears a close rela-

tionship to the degree that malnutrition has served as a precipitating or contributing factor. Usually, as long as the patient relishes and digests an adequate, well balanced diet little is to be gained by distorting the menu, and supplements are rarely indicated unless food intake is inadequate or when persistent fatty infiltration of liver cells is demonstrable. Further critical studies on the indications and limitations of dietary regulation in various types of liver disease are very much indicated.

Adequate rest is often neglected as a therapeutic measure. Fatigue and muscular exertion increase the metabolic demands on the liver and depress many of its functional capacities. The recent studies of Bradley indicate that exercise and even upright posture decrease the portal blood flow significantly. When the intralobular circulation is already impeded by disease, the possibility that physical activity may further decrease oxygenation and nutrition of the hepatic cells must be recognized. Theoretical considerations such as these are borne out in practice by the frequency of relapse in hepatitis when the patient attempts early ambulation and by the experience that the decompensated cirrhotic subject may show little improvement until enforced rest is instituted.

The pathogenesis of hepatic disease also presents many unanswered problems, especially those dealing with progressive cellular degeneration and scarring. Many cases of

cirrhosis cannot be ascribed with certainty to infection or exogenous toxins or to known dietary deficiencies, and yet once the injury is initiated the process may continue despite all types of medical management.

Despite the many difficulties in making exact studies of the liver and its disorders the field is not static. New hepatic activities are still being described and familiar ones are being re-evaluated by isotope studies and by improved analytic technics. Serial biopsies are now widely employed in the correlation of anatomic lesions with functional derangements and in observation of the course of disease under controlled conditions. Methods for localizing certain enzymatic activities to various parts of the hepatic unit have recently been devised and are being applied to clinical problems. The effect of the newer antibiotics on the hepatotropic viruses is under intensive study. The nature of the changes in the serum protein-lipid complex found in infectious hepatitis and in other inflammatory conditions of the liver is subject to further study from many angles. Splanchnic hypertension is being successfully treated surgically by shunting portal blood into the vena cava; studies on these patients may throw further light on circulatory factors in cirrhosis and other hepatic derangements. Improvement in diagnosis and management can therefore be predicted with confidence in this difficult clinical field.

FRANKLIN M. HANGER, M.D.

Presbyterian Hospital, N. Y., N. Y.

Clinical Studies

Correlation of Liver Function and Liver Structure*

Clinical Applications

HANS POPPER, M.D., FREDERICK STEIGMANN, M.D., KARL A. MEYER, M.D.,
DONALD D. KOZOLL, M.D. and MURRAY FRANKLIN, M.D.

Chicago, Illinois

THE study of liver diseases has hitherto relied chiefly upon two sources of information: physiologic examination of liver function and morphologic study of necropsy material. In the past thirty years a large number of liver function tests, based on some of the almost innumerable functions of the liver, has been described. However, the diagnostic interpretation of the several tests still involves theoretical and practical difficulties. Recent attempts to use composite liver function tests¹⁻⁴ have somewhat clarified the picture. Nevertheless, there remain many cases in which performance of a multitude of liver function tests does not lead to a definite diagnosis. Correlation of observations at autopsy with clinical and laboratory findings, too, is in many instances unsatisfactory, especially in acute liver damage. Thus, in some instances in which the pathologist reports impressive but localized alterations, such as central and especially focal necrosis, functional and clinical changes may be insignificant whereas in other instances in which the structural changes are inconspicuous but diffuse, liver function is severely impaired.

The results of liver function tests carried out days or weeks before autopsy cannot be expected to correlate closely with the morphologic findings at necropsy. The liver of the cadaver—even if the necropsy is done

shortly after death—may show a quite different morphologic picture when compared with the “living” liver tissue obtained by aspiration biopsy, as we could establish in a few examples in which biopsies were performed a few hours before death. The former showed widespread breakup of the liver cell cords and marked widening of the perisinusoidal tissue spaces not seen in the latter. It was also found that in previously healthy individuals dying instantaneously, e.g., in a crash, the liver tissue spaces were not visible, in contrast to the open perisinusoidal spaces usually seen in persons who died within one hour after an accident. Agonal changes, therefore, may significantly alter the morphologic picture of the liver.^{4a} Consequently the recently expanded use of liver biopsy⁵⁻¹¹ (excision during laparotomy or peritoneoscopy or by needle aspiration) has made possible better correlation of the structural and functional alterations in different stages of liver disease. Such correlation, applied to the interpretation of both morphologic alteration and functional derangement, should lead to improved diagnosis and management in liver disease.

This presentation concerns itself with a study of liver biopsies in relation to four problems: (1) Correlation of different liver function tests with various histopathologic phenomena independent of the underlying

* From The Hektoen Institute for Medical Research, Cook County Hospital, Chicago, Ill. Presented as a Scientific Exhibit at the Centennial Session of the American Medical Association, Atlantic City, N. J., June, 1947. Supported by a grant from the Dr. Jerome D. Solomon Memorial Research Foundation.

disease. (2) Clinical classification of liver diseases on a morphologic basis. (3) Evaluation of the practical improvement in the differential diagnosis of liver disease by the addition of liver biopsy to clinical and functional examinations and (4) Combined functional and morphologic evaluation of therapeutic procedures in liver disease.

METHODS IN LIVER FUNCTION TESTS

The results of a series of sixteen liver function tests were correlated in each case with liver biopsy. The tests employed can be classified and interpreted as follows:

Tests Indicating Liver Cell Damage. 1. *Brom-sulfalein retention:* A retention of more than 6 per cent forty-five minutes after the injection of 5 mg. of dye per Kg. of body weight was considered pathologic due to decreased clearance of the blood from the dye.¹² This test is valuable only in the absence of conspicuous jaundice.

2. *Cephalin-cholesterol flocculation:*¹³ A flocculation greater than 1 plus was considered pathologic, indicative of increased gamma globulin and reduced albumin. This test is rather sensitive and of great practical help in the differential diagnosis of jaundice since it is usually negative in extrahepatic biliary obstruction, even with much liver damage, except when there is associated infection.

3. *Thymol turbidity test:*^{14,15} A turbidity of more than 4 units was taken as pathologic. It indicates increase of lipids and of gamma or beta globulins or lipid protein complexes migrating with them, possibly associated with reduction of the albumin fraction.^{15a} This test is a valuable supplement to the cephalin-cholesterol flocculation test.

4. *Albumin-globulin ratio:* In liver disease a ratio of less than 1.2 was taken as evidence of either reduced synthesis of albumin or increased formation of globulin by the reticulo-endothelial system. Obviously other factors, such as loss of albumin in the urine, may affect the ratio.

5. *Hippuric acid excretion:*¹⁶ The inability of the liver to detoxify and excrete as hippuric acid in the urine more than 0.7 to 1.0 Gm. of a 1.7 Gm. dose of sodium benzoate injected intravenously was considered pathologic. This test is of no value in the presence of renal damage. It is of limited value but useful, especially in acute liver disease.

6. *Cholesterol ester-cholesterol ratio:* The inability to esterify more than 60 per cent of the total serum cholesterol was interpreted as liver damage. The commonly used Bloor method¹⁷ does not yield altogether reliable results whereas the method of Schoenheimer and Sperry¹⁸ is rather elaborate for routine examination. Nevertheless, the cholesterol ester-cholesterol ratio is valuable, especially for quantitative follow-up of the degree of liver damage.

7. *Plasma vitamin A:* Levels of less than 15 micrograms per 100 cc. of plasma were taken as signs of blocked release of vitamin A from the liver to the blood in acute liver damage; in chronic liver disease impaired intestinal absorption is an additional factor.¹⁹⁻²¹ Faulty general nutrition is responsible less often for reduced plasma vitamin A level. Consequently, a reduced level may under certain circumstances, be of diagnostic value, especially in following the clinical course of a patient.

8. *Total serum proteins:* Less than 6.0 Gm. per cent was considered abnormal but not necessarily indicative of liver cell damage since other factors (such as loss of protein in urine, or starvation) may cause a low serum protein. This determination aids primarily in establishing the therapeutic protein requirements.

Tests for Marked Interference with Bile Flow. 1. *Fecal urobilinogen:*²² Excretion of less than 10 mg. of urobilinogen per 100 Gm. of feces indicates lack of secretion of its precursor, bilirubin, into the intestine, as seen in biliary obstruction.

2. *Serum alkaline phosphatase:*²³ Values above 4 Bodansky units indicate either reduced biliary excretion of the enzyme into the intestine or increased production within the liver, provided that excess osteoblastic formation in various bone diseases is ruled out. Levels above 15 units usually point to extrahepatic obstruction. Values between 4 and 15 units are found more often in hepatitis or cirrhosis.

3. *Total serum cholesterol:*²⁴ In a jaundiced patient a level above 250 mg. per cent is considered due to reduced biliary excretion, provided other factors of hypercholesterolemia are excluded (e.g., hypothyroidism, pregnancy, nephrosis, xanthomatosis).

Tests for Either Disturbed Liver Cell Function and/or Marked Interference with Bile Flow. 1. *Urinary urobilinogen:* Urinary urobilinogen is normally excreted in amounts of 1 to 3 mg. per day²⁵ or 1 to 3 units in a two-hour sample.²² This quantity is decreased in biliary obstruction

because of decreased formation of urobilinogen in the intestine and subsequent reduced reabsorption. It is increased in the urine in liver damage due to failure of the damaged liver cells to re-excrete the urobilinogen absorbed from the intestine. Urinary urobilinogen is also increased in hemolytic processes. The determination of urobilinogen in the urine is simple and if performed daily may be of great diagnostic value. Incomplete obstruction, as in choledocholithiasis, gives fluctuating values.

2. *Prothrombin time percentage*:²⁶ This is reduced below 85 per cent of normal by inadequate absorption of vitamin K from the intestine and/or reduced synthesis of prothrombin by the liver cells. Only the former condition (as in obstructive jaundice) gives a sustained response to parenteral vitamin K therapy. The therapeutic test may, therefore, under some circumstances aid in establishing liver damage.

3. *Total serum bilirubin*:²⁷ Elevation above 1.2 mg. per cent signifies retention of bilirubin in the blood stream or, more commonly, its regurgitation from the smallest biliary passages into the blood. The determination aids more in following the course of liver disease than in differential diagnosis.

Test for Portal Inflammation. Sedimentation rate: When elevated above 15 mm./hr. in liver diseases, inflammatory changes in the portal triads were assumed, provided that other inflammatory foci were excluded.

Test for Hepatorenal Relation. Serum non-protein nitrogen: Values above 40 mg. per cent may be found associated with liver damage and are then due to increased reabsorption of nitrogenous substances in the renal tubules, provided that primary renal causes are excluded.²⁸ Such pathologic reabsorption occurs more often in toxic hepatitis or biliary obstruction of long duration than in other types of liver disease.

METHODS IN LIVER BIOPSIES

The majority of liver biopsies in this study were procured by means of a Turkel needle²⁹ inserted under local anesthesia through the seventh to ninth right costal interspace in the mid-axillary line. The patient was placed in the left lateral decubitus position with a pillow under the left flank to act as a "gallbladder rest." This approach assured displacement of all viscera and ascitic fluid. The Turkel needle consists essentially of an outer trocar needle

for insertion through the parietes, with an inner serrated trephine which cuts a core of tissue approximately 2 mm. in diameter. A syringe is attached upon removing the trephine needle to aspirate the tissue core. Others have used the Vim-Silverman needle. This study is now being continued with the use of Gillman's technic.⁹

The biopsy material was fixed in Zenker-formalin or Carnoy's solution. Sections were stained with hematoxylin-eosin, Mallory's aniline blue connective tissue stain and Gomori's reticulum fiber stain.

Because of the danger of fatal hemorrhage from this procedure⁷ the following conditions are considered, for the present, as contraindications to liver biopsy; increasing experience may alter this list: (1) Hypoprothrombinemia (prothrombin time percentage under 85); (2) severe cholemia; (3) passive congestion of the liver; (4) systemic hypertension of marked degree; (5) hemorrhagic diseases; (6) atrophic liver (difficulty in engaging liver with needle).

This study includes our experience with 221 needle biopsies obtained in 154 patients and 106 biopsies obtained during laparotomy.

OBSERVATIONS ON CORRELATION OF LIVER FUNCTION TESTS WITH SEVERAL STRUCTURAL PHENOMENA

As presented in detail in another publication³⁰ the following conclusions can be drawn from correlations made out between certain morphologic phenomena and abnormal results of liver function tests. These correlations were obtained by statistical methods without taking into account the diagnosis in each individual case. They represent association of phenomena rather than necessarily cause and effect relationships. (Table I.)

A significant correlation was found between diffuse liver cell damage and bromsulphalein retention, cephalin-cholesterol flocculation, thymol turbidity and albumin-globulin ratio. A lesser degree of correlation was observed with marked elevation of serum bilirubin, reduction of plasma vitamin A and increase in prothrombin time percentage. No correlations were evident between diffuse liver cell damage and total serum protein, alkaline phosphatase, total cholesterol and cholesterol esters, urinary

and fecal urobilinogen, nonprotein nitrogen and sedimentation rate.

Focal necrosis, in sharp contrast to diffuse parenchymal damage, showed little correlation with any of the liver function tests performed.

function tests. Histologically impressive focal necroses, however, may not be mirrored at all by function tests because the surrounding intact liver parenchyma compensates for the damaged cells. Liver diseases with circumscribed lesions, such as

TABLE I
STATISTICAL RELATION BETWEEN LIVER FUNCTION TESTS AND PATHOLOGIC PHENOMENA
WITHOUT REFERENCE TO DIAGNOSIS

	Diffuse Liver Cell Damage	Focal Necrosis	Regener- ation	Distorted Recon- struction	Periportal Inflam- matory Activity	Fatty Metamor- phosis	Kupffer Cell Activity
Cephalin-cholesterol flocculation.....	+++	0	0	+++	±	0	0
Thymol turbidity.....	+++	0	++	++	0	0	0
Reduction of total serum protein.....	0	0	0	0	0	0	0
Abnormal serum albumin-globulin ratio.....	+++	0	0	0	0	0	+++
Elevated serum N.P.N.	0	0	0	0	0	0	0
Elevated urinary urobilinogen.....	0	0	0	0	0	0	0
Reduced stool urobilinogen.....	0	0	0	0	0	0	0
Elevated total serum cholesterol.....	0	0	0	0	0	0	0
Reduced cholesterol ester ratio.....	0	0	0	0	0	0	0
Serum bilirubin elevated above 8 mg. per cent.....	+	0	0	0	0	0	+++
Bromsulphalein retention.....	+++	0	0	0	0	0	0
Reduced hippuric acid synthesis.....	0	0	0	0	0	0	0
Elevated serum alkaline phosphatase...	0	0	0	0	0	0	0
Reduced prothrombin time percentage.	+	0	0	0	0	0	0
Reduced plasma vitamin A.....	+	0	0	0	0	0	0
Elevated sedimentation rate.....	0	0	0	++	++	0	0

Regeneration of individual liver cells showed a significant correlation with thymol turbidity.

Distorted reconstruction of the lobular pattern, as seen in cirrhosis, revealed a significant degree of correlation with the cephalin-cholesterol flocculation, thymol turbidity and elevation of the sedimentation rate.

Periportal inflammatory activity showed a significant correlation with increased sedimentation rate.

Fatty metamorphosis of the liver was not statistically correlated with any of the liver function tests employed.

Kupffer cell activity was found related to elevated serum bilirubin and pathologic albumin-globulin ratio.

It should be emphasized that diffuse liver cell damage, although morphologically often not conspicuous, is usually associated with markedly abnormal results in many

granulomas, abscesses (e.g., amebic), tumor metastases or other local alterations which do not influence the surrounding liver parenchyma, may not be disclosed by liver function tests.

MORPHOLOGIC CLASSIFICATION OF DIFFUSE PARENCHYMAL LIVER DAMAGE

Although its inflammatory character in many cases is not established, acute parenchymal liver damage, if clinically conspicuous, is referred to as hepatitis. Hepatitis may be classified in two types: primary or medical form due to various infections and intoxications, and a secondary or surgical form due to tumors, scars and strictures involving the biliary tract. In the following enumeration of the most commonly encountered forms the clinical and morphologic findings are summarized and the laboratory tests listed in the order of

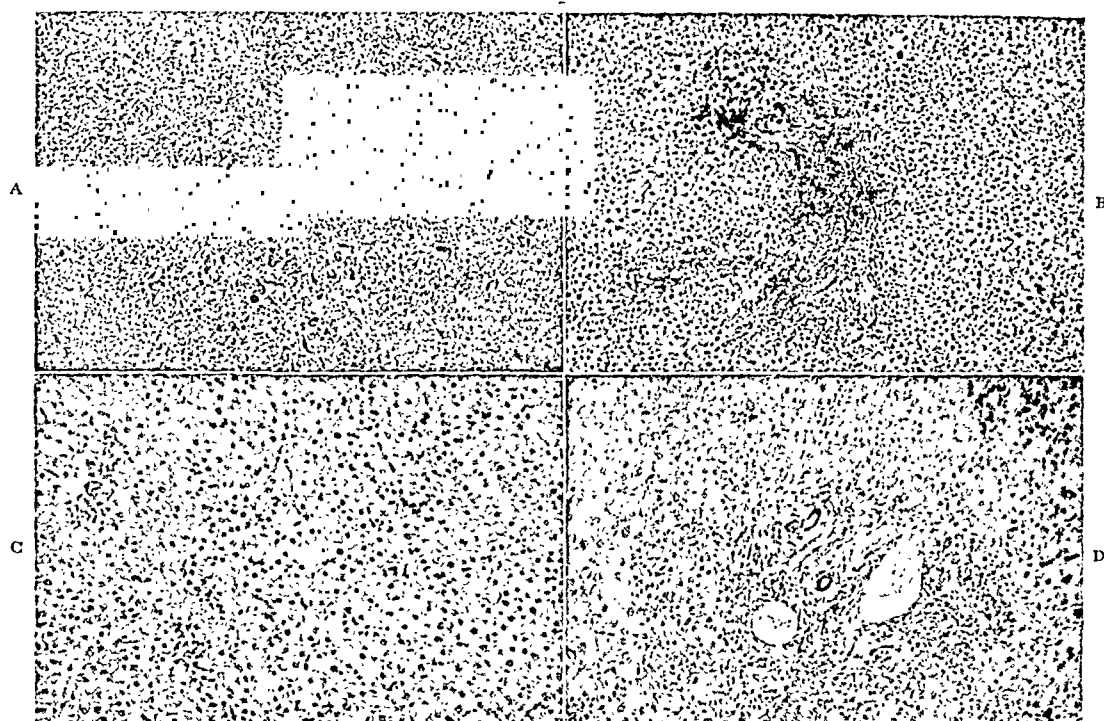


FIG. 1. A, autopsy specimen of an acute fulminating form of viral (infectious) hepatitis. The liver cells have almost completely disappeared except for a few regenerates which simulate proliferated bile ducts. Phagocytosing, chiefly histiocytic, exudate cells are seen in the lobular framework and portal triads. B, biopsy specimen of a severe (non-fatal) form of viral hepatitis. The liver cells are irregularly stained and poorly outlined; occasionally they are hyalinized. The nuclei vary in size. Round cells are seen in sinusoids and in large numbers in portal triads. C, biopsy specimen of mild viral hepatitis. The liver cell cords are irregularly arranged and their cells vary in size. Throughout the parenchyma and portal triads many mononuclear cells are seen. D, biopsy specimen of viral hepatitis with protracted convalescence. The poorly delineated portal triads reveal marked cellular infiltration and early fibrosis. Around them regeneration of liver cells is conspicuous.

significance. However, it is not implied that the results of liver function tests permit a histopathologic diagnosis.

Primary Hepatitis. 1. *Infectious or viral hepatitis:* At least two portals of entry are recognized: an oral route with an incubation period of two to six weeks and a parenteral route (homologous serum jaundice) with an incubation period of two to six months.³⁷ The following main types of this disease are observed:

The fulminant form^{32,33} is often seen in homologous serum jaundice and is fatal in less than ten days after onset of icterus. Histologically, (Fig. 1A) an "explosive" destruction of almost all liver cells is seen with little remaining that resembles the normal liver architecture. There is marked inflammatory reaction and phagocytosis. This is one of the types formerly referred to as "acute yellow atrophy." Most of the

liver function tests are abnormal, especially the cephalin-cholesterol flocculation and thymol turbidity; serum bilirubin, prothrombin time and (usually) urinary urobilinogen are markedly elevated. In addition there is a decrease of plasma vitamin A, hippuric acid synthesis, cholesterol ester-cholesterol and albumin-globulin ratios. The sedimentation rate is increased.

In the prodromal period of the severe (non-fatal) form, often prolonged, febrile or gastrointestinal symptoms predominate. The course is stormy and jaundice usually lasts about four weeks, resulting in considerable weight loss and weakness. Results of the liver function tests are similar to those in the previous form. In addition, the alkaline phosphatase is usually elevated. Histologically, (Fig. 1B) there is diffuse damage of the liver cells with considerable mesenchymal reaction as indicated by diffuse intralobular

and periportal infiltration with phagocytic round cells.

In the mild form jaundice may be absent. It is, therefore, not infrequently missed because of its clinically inconspicuous course. Only a few of the liver function tests are abnormal. There is usually retention of bromsulfalein, increase of urinary urobilinogen and increase in the sedimentation rate. Cephalin-cholesterol flocculation and thymol turbidity may be abnormal. In addition hippuric acid synthesis and cholesterol esters are occasionally reduced. Liver biopsy (Fig. 1c) shows diffuse but milder liver cell damage and not very conspicuous intralobular and periportal mesenchymal reaction.

In the protracted stage icterus is usually absent and symptoms of fat intolerance and neurasthenia predominate. A transition to cirrhosis may occur. Only the thymol turbidity and sedimentation rate may be abnormal. Liver biopsy (Fig. 1d) often reveals more than anticipated from the clinical picture. Liver cell damage is slight but signs of regeneration of parenchymal cells with portal fibrosis and round cell infiltration suggest a chronic phase of the disease.

Absence of bile from the duodenum may occur in any stage of hepatitis, leading to a clinical syndrome similar to extrahepatic biliary obstruction. Serum bilirubin, total cholesterol, alkaline phosphatase and sedimentation rate are high while the urinary and fecal urobilinogen are markedly decreased. Results of the other function tests will depend on the type of hepatitis associated with this phenomenon. In the acute stage they are usually abnormal; in the late, protracted form of viral hepatitis (transition into cholangiolitic cirrhosis of Hoffbauer and Watson³⁴) they may be normal. There is no characteristic histologic picture for the intrahepatic biliary arrest *per se*. Morphologically, the picture will depend on the stage of hepatitis, independent of the arrest of bile flow.³⁵

2. *Toxic hepatitis*: This comprises conditions caused by substances known to be in-

jurious to the liver such as exogenous agents (chemicals, drugs and bacteria such as pneumococci, salmonella) or endogenous toxins (e.g., in pregnancy, hyperthyroidism, etc.). In a large number of patients with morphologically identical lesions no hepatotoxic factor can be elicited in the history.

In the fatal form prodromal symptoms are variable but the course is stormy and rapid with death in cholemia and uremia. Most liver function tests give abnormal results. However, the cephalin-cholesterol flocculation and thymol turbidity tests are not always positive. Prothrombin time, serum bilirubin, urinary urobilinogen, non-protein nitrogen and sedimentation rate may be increased. Albumin-globulin and cholesterol ester ratios and plasma vitamin A are decreased. Histologically, in the most common form, there is widespread necrosis of liver cells in the central zone (Fig. 2A) without much evidence of mesenchymal reaction. This picture is often referred to as central necrosis.

In the severe (non-fatal) form the prodromal symptoms may be prolonged. The clinical course and results of liver function tests are similar to those in the fatal form but the patient recovers slowly. Morphologically, (Fig. 2b) gradual cell death and disappearance of liver cells occurs in zonal arrangement, usually in the center of the lobule, but little mesenchymal reaction is noted.

The fatty form is frequently called fatty degeneration and is often the result of a known hepatotoxic substance, at times predisposed by nutritional deficiency. Results of the liver function tests are similar to those in the two previous forms of toxic hepatitis. Liver biopsy (Fig. 2c) shows diffuse fatty metamorphosis with necrobiosis of liver cells without marked mesenchymal reaction.

In the mild form there is no characteristic prodromal state and the clinical course is characterized by prolonged, often mild jaundice. Urinary urobilinogen is high and serum bilirubin slightly increased. There is retention of bromsulfalein. The flocculation tests may be positive. In addition hippuric

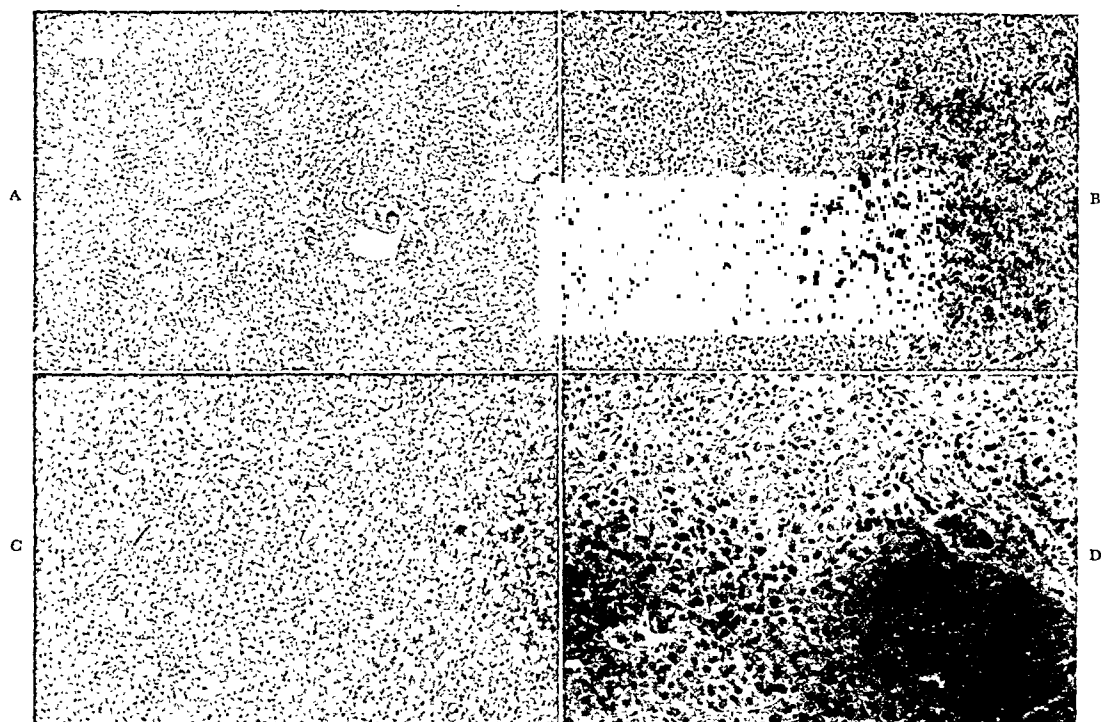


FIG. 2. A, autopsy specimen of toxic hepatitis. The liver cells in the lobular centers have disappeared and the cells on the border of the denuded areas are necrobiotic. Little mesenchymal reaction is seen. B, biopsy specimen of severe (non-fatal) toxic hepatitis. There is coagulation necrosis and vacuolization of epithelial cells in the center of the lobules, with moderate regeneration and little mesenchymal reaction. C, biopsy specimen of fatty toxic hepatitis. There is extensive fatty metamorphosis with coagulation necrosis, necrobiosis and bile pigment imbibition of liver cells. The Kupffer cells are hardly mobilized. D, biopsy specimen of mild toxic hepatitis. The staining qualities of the liver cells are irregular throughout. Liver cell cords and portal triads are almost devoid of cellular reaction.

acid synthesis and cholesterol ester ratio may be decreased. In the liver biopsy (Fig. 2D) diffuse or centrolobular damage is seen, mild in degree, associated with focal necrosis with almost no mesenchymal response.

Secondary Hepatitis. In secondary hepatitis occurring in surgical conditions of the biliary tract caused by tumors, stones or strictures, liver damage is due either to prolonged biliary obstruction (biliary hepatitis) or to bacterial infection of the portal triads (purulent hepatitis).

1. **Biliary hepatitis:** Liver cell damage with impaired function is due to biliary stasis. The extent of biliary hepatitis depends on the degree and duration of the obstruction. It is, therefore, rather common in malignant obstruction of the bile ducts which is usually complete and permanent.

The early form occurs in the first weeks of obstruction and may be associated with pruritus. Fecal and urinary urobilinogen

are absent while serum bilirubin, alkaline phosphatase, total cholesterol, prothrombin time and sedimentation rate are increased. The thymol turbidity is slightly increased but the cephalin-cholesterol flocculation test is negative. Liver biopsy (Fig. 3A) shows bile stasis and bile impregnation of the liver cells in the center of the lobules with slight liver cell damage.

The advanced form is usually the result of several weeks of complete biliary obstruction. The patient is cachectic, has acholic stools, at times a palpable gall-bladder and may be cholemic. The same tests are positive as in the earlier stage. In addition there is reduction of hippuric acid synthesis, of total protein, of albumin-globulin and cholesterol ester ratios; non-protein nitrogen is often increased. Biopsy (Fig. 3C) reveals bile casts in the central and peripheral portions of the lobule with a significant degree of diffuse liver cell damage and circumscribed necroses with

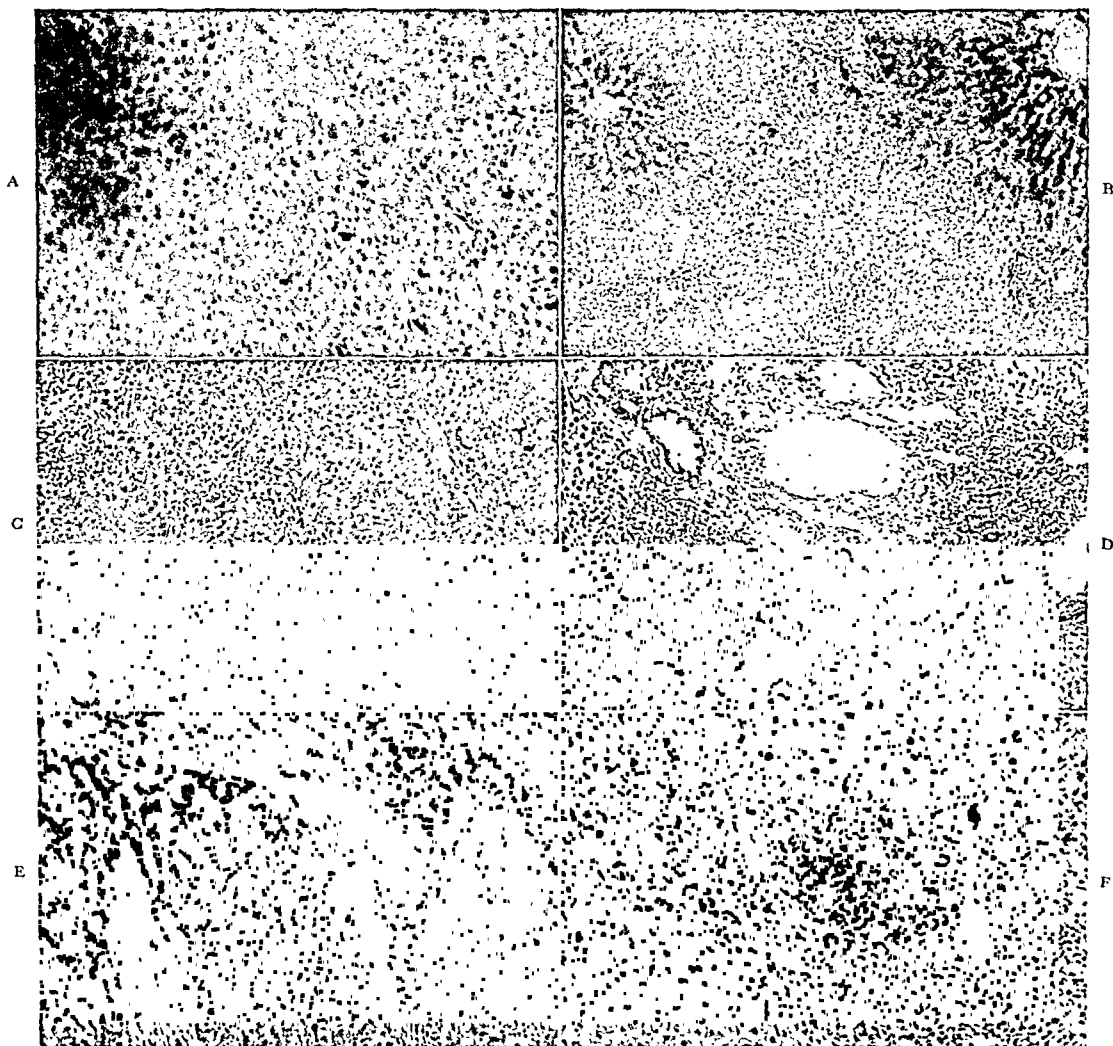


FIG. 3. A, biopsy specimen of early biliary hepatitis. There are bile thrombi in the center of the lobules, with little liver cell damage in the adjoining areas and almost no mesenchymal reaction. B, biopsy specimen of a case of portal perilymphangitis. Lymphocytes and histiocytes are seen around lymphatics of the portal triads. Bile ducts, vessels and liver parenchyma reveal no abnormal changes. C, biopsy specimen of severe biliary hepatitis. Bile thrombi are seen in central and periportal areas of the lobule. There is diffuse liver cell damage and enlargement of the portal triads due to circular fibrosis. D, biopsy specimen of purulent hepatitis showing perilymphangitic accumulations of round cells and polymorphonuclear cells in enlarged portal triads. The latter are not sharply limited and reveal bile duct proliferation. E, biopsy specimen of a chronic form of biliary hepatitis. Proliferated connective tissue with bile ducts surround the parenchyma in which distorted reconstruction has started. Some liver cell damage is noted. F, biopsy specimen of a chronic form of purulent hepatitis. There is dense cellular infiltration of the enlarged and fibrosed portal triads which reveal proliferating bile ducts. The liver parenchyma shows little damage.

bile imbibition (bile infarcts). The periportal fields show circular fibrosis.

The chronic cirrhotic form represents the late stage of an obstruction, usually malignant, with dark green icterus, pruritus, cachexia, anemia, large liver, occasionally palpable gallbladder but rarely ascites. The same tests are positive as in the preceding forms and plasma vitamin A is also reduced. Morphologically, (Fig. 3E) there is portal

fibrosis, bile stasis and partially distorted reconstruction of the lobular pattern. Usually liver cell damage is marked.

2. *Purulent hepatitis*: Bacterial infection of the portal triads develops through hematogenous, hemolymphatic or cholangitic routes. It occurs in various inflammatory lesions in the portal system independent of degree or duration of biliary obstruction. It may, therefore, complicate any stage of

surgical jaundice, but most often the benign form.

The perilymphangitic form may occur in any intra-abdominal condition in which irritating material reaches the liver, e.g., in cholecystitis without jaundice or other gastrointestinal lesions. The clinical picture is not characteristic. The sedimentation rate is usually increased. Biopsy of the liver (Fig. 3B) shows accumulations of round cells and occasional polymorphonuclear leukocytes around the lymphatics of the portal triads, frequently without evidence of liver cell damage.

The suppurative form is clinically characterized by chills, fever and leukocytosis, as seen with cholangitis or Charcot's intermittent hepatic fever. In contrast to the biliary form the cephalin-cholesterol flocculation and thymol turbidity tests are both positive. Serum bilirubin is not always elevated, there is bromsulfalein retention, increase in urinary urobilinogen and sedimentation rate and usually reversal of the albumin-globulin ratio. In more severe cases the cholesterol ester ratio, hippuric acid synthesis and plasma vitamin A are reduced. Biopsy (Fig. 3D) reveals multiple purulent foci or abscesses in the portal triads and diffuse liver cell damage.

The chronic form is usually seen clinically after prolonged incomplete obstructive jaundice in the presence of inflammation, e.g., from a stricture of the bile ducts. There are bouts of chills, fever and leukocytosis with development of a large firm liver, large spleen and anemia. The cephalin-cholesterol flocculation and thymol turbidity tests are positive. Serum bilirubin, urinary urobilinogen, prothrombin time and sedimentation rate are increased; the total serum protein is reduced. In addition there is a decrease in the albumin globulin ratio, plasma vitamin A, cholesterol ester ratio and hippuric acid synthesis. Morphologically, (Fig. 3F) there is portal fibrosis with dense infiltration by inflammatory cells. Liver cell damage is evident. The lobular pattern shows some distorted reconstruction.

Cirrhosis. This is a group of chronic liver

diseases or hepatitis of varying etiology. Connective tissue proliferation and distorted reconstruction of the lobular pattern resulting in more or less portal hypertension are significant features. Some types are related to the forms of hepatitis already described.

1. *Portal Cirrhosis without Jaundice.* This is the type originally described by Laennec. Its etiology is as yet unestablished although nutritional deficiencies with or without alcohol addiction seem to play a rôle. There is an insidious onset and in later stages, subicterus, ascites, esophageal varices, spider nevi, splenomegaly and anemia appear. The albumin-globulin ratio and total serum protein are decreased. There is bromsulfalein retention. The cephalin-cholesterol flocculation and thymol turbidity tests are often positive. The sedimentation rate and urinary urobilinogen are increased. In addition hippuric acid synthesis may be reduced. Biopsy (Fig. 4A) reveals a progressive portal fibrosis, distorted reconstruction—often complete—of the lobular pattern usually without marked liver cell damage.

2. *Portal Cirrhosis with Jaundice.* Here the clinical picture is complicated by icterus and occasionally even by cholemia. In addition to the abnormal liver function tests there is a marked increase in serum bilirubin, prothrombin time and usually non-protein nitrogen. In addition the cholesterol ester ratio, hippuric acid synthesis and (often) plasma vitamin A are reduced, the serum alkaline phosphatase is elevated. Morphologically, (Fig. 4B) in addition to the histologic picture of portal cirrhosis just described, the liver cells in the nodules are found to be diffusely damaged and there are many bile casts. Occasionally a cholestatic phase occurs in this form, characterized by absence of urobilinogen from urine and feces, by high total cholesterol and extremely high alkaline phosphatase. In this phase encircling fibrosis around the small bile ducts and severe bile stasis is noted histologically.

3. *Fatty Cirrhosis.* This is now considered the result of a nutritional deficiency (ab-

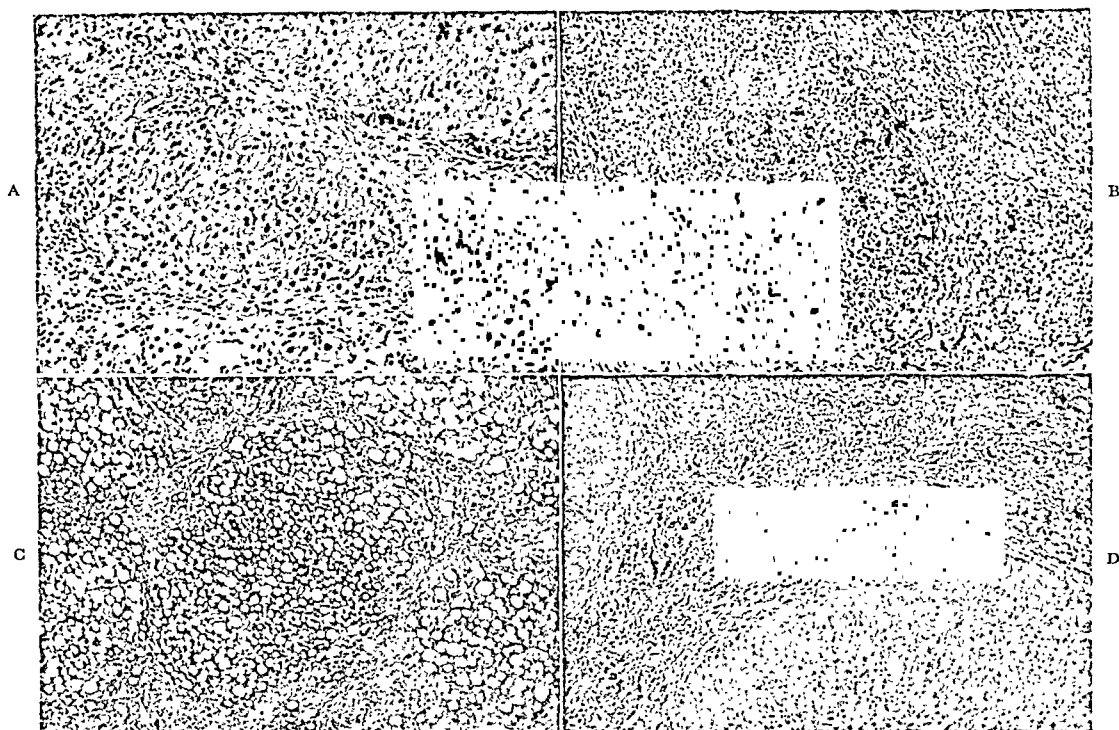


FIG. 4. A, biopsy specimen of portal cirrhosis without jaundice. Nodules of a variable size contain almost intact liver cells. The nodules are surrounded by narrow connective tissue bands, with cellular infiltration and proliferating bile ducts. B, biopsy specimen of portal cirrhosis with jaundice. The nodules are not sharply demarcated from the connective tissue bands. The liver cells reveal diffuse damage, are dissociated and surround bile casts. C, biopsy specimen of fatty cirrhosis. The liver cells are arranged in nodules of relatively uniform size which are separated by sharply delineated narrow trabeculae. The cells usually contain one large fat droplet. D, biopsy specimen of postnecrotic cirrhosis after viral hepatitis. Various sized nodules are surrounded by wide connective tissue bands containing cord-like liver cell regenerates simulating proliferating bile ducts in addition to vessels and partially phagocytosing mononuclear cells.

sence of lipotropic substances), seen often in alcoholics and characterized clinically by a large liver, slight portal hypertension, subicterus and slight anemia. There is bromsulfalein retention, reduced serum protein and lowered albumin-globulin ratio. Urinary urobilinogen is slightly increased. The cephalin-cholesterol flocculation and thymol turbidity tests may or may not be positive. In some cases the sedimentation rate is increased and the cholesterol ester ratio reduced. Biopsy (Fig. 4c) reveals diffuse fatty metamorphosis and beginning distorted reconstruction of the lobular pattern but little evidence of liver cell necrosis.

4. *Postnecrotic cirrhosis.* This is thought to be the sequel of chronic viral hepatitis or, less commonly, of toxic hepatitis. The clinical picture is that of cirrhosis (portal hypertension, anemia and spider nevi) with more or less severe jaundice. The cephalin-

cholesterol flocculation and thymol turbidity tests are positive, serum bilirubin, prothrombin time and urinary urobilinogen

TABLE II
IMPROVEMENT IN DIAGNOSIS OF LIVER DISEASES BY THE USE
OF A SERIES OF LIVER FUNCTION TESTS AND LIVER BIOPSY

Final Diagnosis	No. of Cases	Percentage of Correct Diagnoses Based on		
		Clinical Observation	Clinical Observation Plus Liver Function Tests	Clinical Observation, Liver Function Tests and Biopsy
Infectious hepatitis	29	86	90	93
Toxic hepatitis	35	57	68	91
Cirrhosis with jaundice	52	77	92	98
Cirrhosis without jaundice	18	83	94	100
Benign obstruction	27	55	85	89
Malignant obstruction	31	74	96	96

are elevated. The total serum protein is reduced and the albumin-globulin ratio is reversed. There is also a reduction of

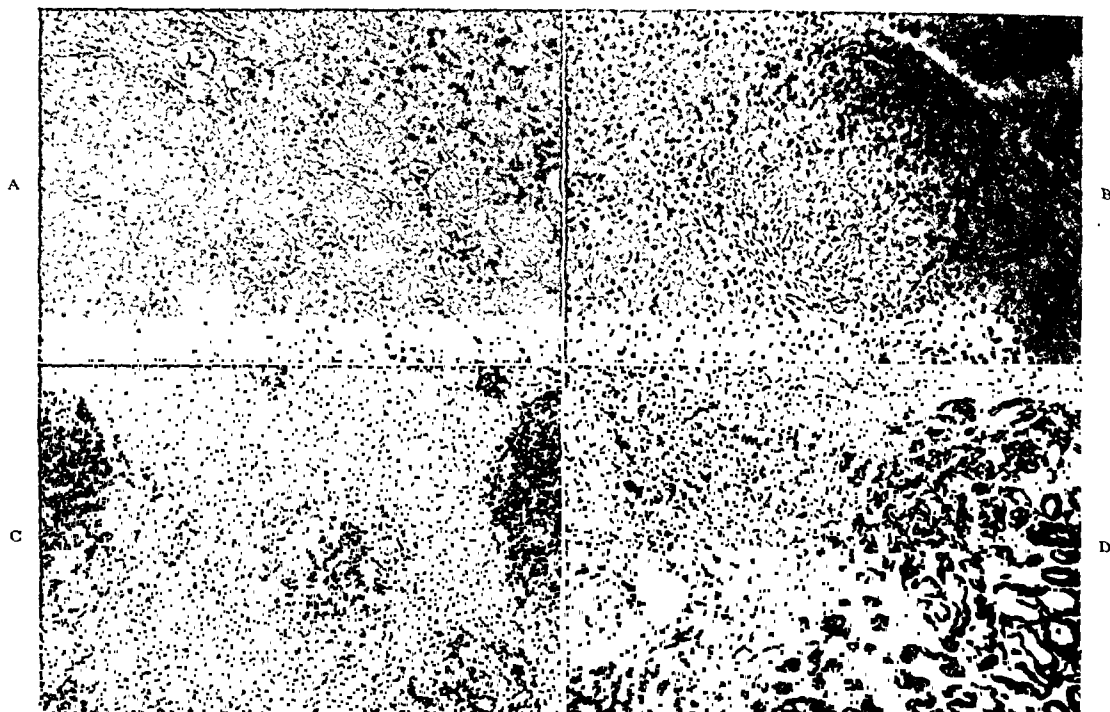


FIG. 5. A, biopsy specimen from a patient with hepatomegaly which proved to be due to amyloidosis. Extensive deposits of pinkish-staining amyloid separate the sinusoids from the compressed liver cell cords. The liver cells themselves reveal little changes. B, biopsy specimen from a patient with Boeck's sarcoidosis. A tubercle is seen composed of epithelioid cells in palisade arrangement, with preserved capillaries in the center and lymphocytes in the outer zone. C, biopsy specimen from a patient with lymphosarcoma. Accumulations of lymphoblastic elements surround vessels and bile ducts in the portal triads. The cellular accumulations are well delineated from the liver parenchyma. D, biopsy specimen of a metastatic adenocarcinoma. The tumor compresses the liver cell cords in the center of which bile thrombi may be seen.

plasma vitamin A, cholesterol ester ratio and hippuric acid synthesis. The sedimentation rate is elevated. Morphologically, (Fig. 4D) the connective tissue in wide areas appears collapsed after the disappearance of liver parenchyma due to extensive necrosis. Otherwise, there is more or less diffuse reconstruction of the lobular pattern with progressive liver cell damage.

LIVER FUNCTION TESTS AND LIVER BIOPSY AS AN AID IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE AND/OR HEPATOMEGALY

The combination of liver function tests with clinical observations and simple urinalysis raises considerably the percentage of correct diagnoses of liver diseases with jaundice. In a previous report³⁶ on 563 jaundiced and 112 non-jaundiced patients use of the liver function tests improved the percentage of correct diagnoses from 62 per cent at the time of the first examination of

the patients to 95 per cent after complete clinical and laboratory work-ups. In this series 192 cases were available in which the diagnosis considered final on discharge or death of the patient was compared with (1) the impression obtained from clinical examination only, (2) the diagnosis derived from clinical observation plus the results of liver function tests and (3) the diagnosis based on biopsy findings together with the just mentioned data. (Table II.) In almost all types studied accuracy of the diagnosis was improved by the liver function tests. Liver biopsy was of additional help. The improvement in diagnosis was greatest in toxic hepatitis. In 5.3 per cent of all cases the histologic diagnosis of the biopsy specimen differed from the final diagnosis and was, therefore, probably wrong.

In some conditions associated with hepatomegaly but without disturbance of liver function, jaundice or ascites, the nature of

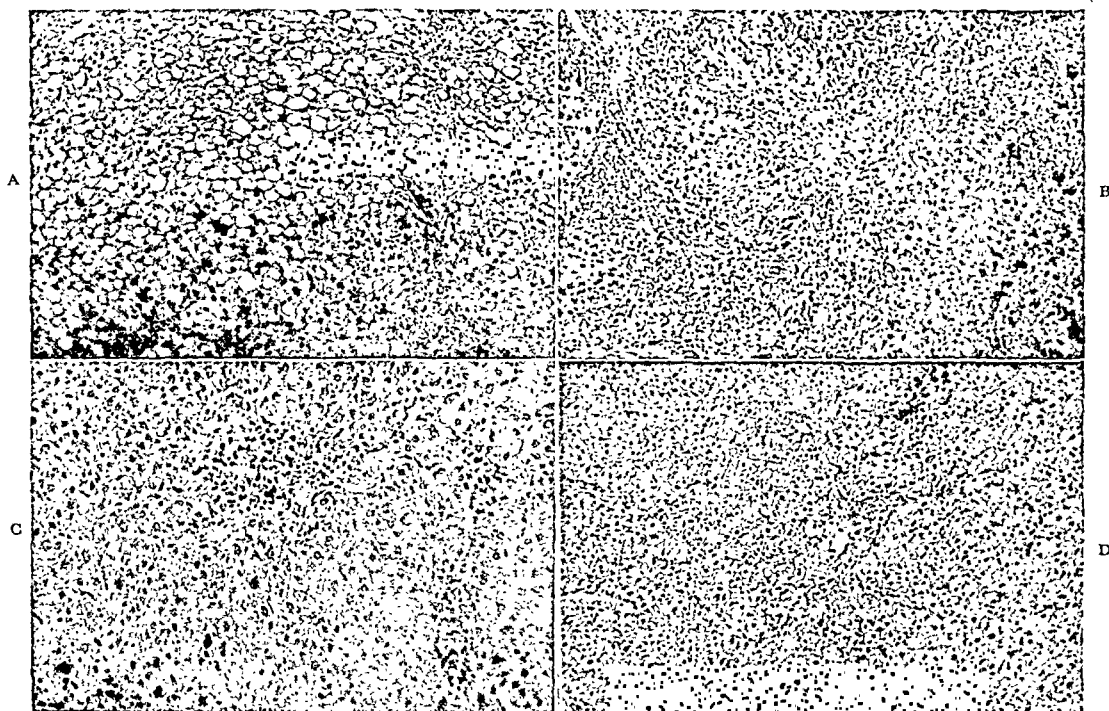


FIG. 6. A, biopsy specimen from a patient with early fatty cirrhosis before lipotropic therapy. Jaundice and hepatosplenomegaly were present; liver function tests were abnormal. Extensive fatty metamorphosis and bile thrombi can be seen; B, biopsy specimen from the same patient as A four weeks after lipotropic therapy. The liver function tests were improved. The liver cells are now fat-free and show signs of cellular regeneration. However, cirrhotic changes such as increased connective tissue with cellular infiltration and proliferating bile ducts are now conspicuous. C, biopsy specimen from a patient with recovering viral hepatitis before start of exercise. Moderate degree of liver cell damage and mesenchymal reaction is present. D, biopsy specimen from the same patient as C taken after three days of controlled exercise. Increase in liver cell damage and mesenchymal reaction is noted. Some liver function tests also showed regression.

the hepatic involvement can be recognized by liver biopsy. In the following instances of this group the diagnosis was first made on the basis of biopsy findings: (1) Amyloidosis (Fig. 5A); (2) Boeck's sarcoidosis (Fig. 5B); (3) lymphosarcoma (Fig. 5C); (4) primary carcinoma of the liver; (5) metastatic carcinoma (Fig. 5D).

This method of diagnosis can also be expected to be of diagnostic help in various storage diseases and in granulomatous or parasitic lesions of the liver.

HISTOLOGIC EVALUATION OF THERAPEUTIC PROCEDURES IN LIVER DISEASES

Evaluation of the morphologic changes occurring after the application of various therapeutic agents may supplement information obtained from clinical and laboratory studies in the human. This help is most valuable since relatively few therapeutic

principles in liver diseases are well established and since clinical and laboratory results are sometimes contradictory.

In addition to the well established principle of administration of a diet of high carbohydrate, high protein, low fat (in acute infectious hepatitis fat may be given as tolerated since the liver is poor in fat) and high vitamins, the intake of methionine (as free amino acid or in protein) or of choline (with or without cystine) has been recommended in recent years.³⁷⁻³⁹ These substances are essential in removal of fat from the liver (lipotropic activity)⁴⁰ by providing labile methyl groups. To methionine, which may be formed in the body from choline and cystine, has also been ascribed a detoxifying effect by providing sulfhydryl groups.⁴¹

While biopsy studies in the human provide additional evidence for the lipotropic

effect of this treatment of fatty livers of various etiology,⁴² they do not necessarily prove that lipotropic therapy is a cure for cirrhosis. In some instances, despite fat removal, the inflammatory process in the portal triads may progress. (Figs. 6A and B.)⁴³

That bed rest is an important adjuvant in the treatment of hepatitis—particularly the infectious type^{44,45}—is emphasized by the marked deterioration of the histologic picture of the liver even in the recovery stage if a biopsy is repeated after exercise. (Figs. 6C and D.)

SUMMARY

1. An attempt has been made to illustrate the aid in diagnosis and management of liver diseases derived from the use of liver function tests and liver biopsy findings, and correlations between them.
2. The significance of a series of liver function tests and the indications and contraindications of liver biopsy in liver disease and other hepatomegalies are briefly discussed.
3. Correlation between morphologic and functional findings helps in evaluation of liver function tests and reveals that most liver function tests give abnormal results in diffuse parenchymal diseases whereas in focal alterations, regardless of severity, none or only a few tests may be pathologic.
4. Based on morphologic and functional criteria, acute hepatic damage was subdivided into viral, toxic, biliary and purulent types; different forms in each group were illustrated by clinical, laboratory and morphologic criteria. The various forms of cirrhosis were similarly discussed.
5. The improvement in diagnosis of liver diseases derived from use of liver function tests and the additional help of liver biopsies is demonstrated. Liver biopsy also can be applied to the critical evaluation of therapeutic procedures in hepatic disease.

REFERENCES

1. WATSON, C. J. and HOFFBAUER, F. S. Liver function in hepatitis. *Ann. Int. Med.*, 26: 813, 1947.

2. GUTMAN, A. B. and HANGER, F. M., JR. Differential diagnosis of jaundice by combined serum phosphatase determination and cephalin flocculation tests. *M. Clin. North America*, 25: 837, 1941.

3. SCHWIMMER, D., KLOTZ, S. D., DREKTER, I. J. and MCGAVACK, T. H. A fasting blood sample procedure in the differential diagnosis and management of hepatic disease. *Am. J. Digest. Dis.*, 12: 1, 1945.

4. MATEER, J., BALTZ, J. E., COMANDURAS, P. E., STEEL, H. M. and BROUWER, S. W. Further advances in liver function tests of the value of a therapeutic test in facilitating the earlier diagnosis and treatment of liver impairment. *Gastroenterology*, 8: 52, 1947.

4(a). POPPER, H. The significance of agonal changes in the human liver. *Arch. Path.*, in press.

5. IVERSEN, P. and ROHOLM, K. On aspiration biopsy of the liver with remarks on its diagnostic significance. *Acta med. Scandinav.*, 102: 119, 1939.

6. DIBLE, J. H., MCMICHAEL, J. and SHERLOCK, S. P. V. Pathology of acute hepatitis: aspiration biopsy studies of epidemic, arsenotherapy and serum jaundice. *Lancet*, 2: 402, 1943.

7. HOFFBAUER, F. W. Needle biopsy of the liver. *J. A. M. A.*, 134: 666, 1947.

8. DAVIS, W. D., SCOTT, R. W. and LUND, H. Z. Needle biopsy of the liver. *Am. J. M. Sc.*, 212: 449, 1946.

9. GILLMAN, T. and GILLMAN, J. A modified liver aspiration biopsy apparatus and technic with special reference to its clinical application as assessed by 500 biopsies. *South African J. M. Sc.*, 10: 53, 1945.

10. MALLORY, T. B. The pathology of epidemic hepatitis. *J. A. M. A.*, 134: 655, 1947.

11. POPPER, H. and FRANKLIN, M. Differential diagnosis of hepatitis by histologic and functional laboratory methods. *J. A. M. A.*, 137: 230, 1948.

12. ROSENTHAL, S. M. and WHITE, E. C. Clinical application of the biomsulphathelin test for hepatic function. *J. A. M. A.*, 84: 1112, 1925.

13. HANGER, F. M. Serologic differentiation of obstructive from hepatogenous jaundice by flocculation of cephalin-cholesterol emulsions. *J. Clin. Investigation*, 18: 261, 1939.

14. MACLAGAN, N. F. The thymol turbidity test: a new indicator of liver dysfunction. *Nature*, 114: 670, 1944.

15. WATSON, C. J., RAPPAPORT, E. M., HAWKINSON, V. and GIEBENHAIN, M. A comparison of the results obtained with the Hanger cephalin-cholesterol flocculation test and the MacLagen thymol turbidity test in patients with liver disease. *J. Lab. & Clin. Med.*, 30: 983, 1945.

15a. KUNKEL, H. C. and HOAGLAND, C. L. Mechanism and significance of the thymol turbidity test for liver disease. *J. Clin. Investigation*, 26: 1060, 1947.

16. QUICK, A. J. Clinical application of hippuric acid and prothrombin tests. *Am. J. Clin. Path.*, 10: 222, 1940.

17. BLOOR, W. R. and KNUDSON, A. The separate determination of cholesterol and cholesterol esters in a small amount of blood. *J. Biol. Chem.*, 27: 107, 1916.

18. SCHOENHEIMER, R. and SPERRY, W. M. Micro-

- method for the determination of free and combined cholesterol. *J. Biol. Chem.*, 106: 745, 1934.
19. KIMBLE, M. S. Photocolorimetric determination of vitamin A and carotene in human plasma. *J. Lab. & Clin. Med.*, 24: 1055, 1939.
 20. POPPER, H. and STEIGMANN, F. The clinical significance of the plasma vitamin A level. *J. A. M. A.*, 123: 1108, 1943.
 21. POPPER, H., STEIGMANN, F., MEYER, K. A. and ZEVIN, S. S. Relation between hepatic and plasma concentrations of vitamin A in human beings. *Arch. Int. Med.*, 72: 439, 1943.
 22. WATSON, C. J., SCHWARTZ, S., SBOROV, V. and BERTIE, E. A simple method for the quantitative recording of the Ehrlich reaction as carried out with urine and feces. *Am. J. Clin. Path.*, 14: 650, 1944.
 23. BODANSKY, A. Phosphatase studies: determination of serum phosphatase: factors influencing accuracy of determination. *J. Biol. Chem.*, 101: 93, 1933.
 24. BLOOR, W. F. The determination of cholesterol in blood. *J. Biol. Chem.*, 24: 227, 1916.
 25. WATSON, C. J. Studies of urobilinogen. 1. An improved method for the quantitative estimation of urobilinogen in urine and feces. *Am. J. Clin. Path.*, 6: 458, 1936.
 26. QUICK, A. J. Determination of prothrombin. *Proc. Soc. Exper. Biol. & Med.*, 42: 788, 1939.
 27. DUCCI, H. and WATSON, C. J. The quantitative determination of the serum bilirubin with special reference to the prompt reacting and the chloroform-soluble types. *J. Lab. & Clin. Med.*, 30: 293, 1945.
 28. MEYER, K. A., POPPER, H. and STEIGMANN, F. Significance of rise of non-protein nitrogen in medical and surgical jaundice. *J. A. M. A.*, 117: 847, 1941.
 29. TURKEL, H. and BETHEL, F. M. A new and simple instrument for administration of fluids through bone marrow. *War Med.*, 5: 222, 1944.
 30. FRANKLIN, M., POPPER, H., STEIGMANN, F. and KOZOLL, D. D. Relation between structural and functional alterations of the liver. *J. Lab. & Clin. Med.*, 33: 435, 1948.
 31. NEEFE, J. R. Recent advances in the knowledge of "virus hepatitis." *M. Clin. North America*, 30: 1407, 1946.
 32. LUCKÉ, B. The pathology of fatal epidemic hepatitis. *Am. J. Path.*, 20: 471, 1944.
 33. LUCKÉ, B. and MALLORY, T. The fulminant form of epidemic hepatitis. *Am. J. Path.*, 22: 867, 1946.
 34. WATSON, C. J. and HOFFBAUER, F. W. The problem of prolonged hepatitis with particular reference to the cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver. *Ann. Int. Med.*, 25: 195, 1946.
 35. STEIGMANN, F., MEYER, K. A. and POPPER, H. Marked interference with bile flow in hepatitis. *Arch. Surg.*, in press.
 36. STEIGMANN, F., POPPER, H. and MEYER, K. A. Liver function tests in clinical medicine. *J. A. M. A.*, 122: 279, 1943.
 37. GYORGY, P. Experimental hepatic injury. *Am. J. Clin. Path.*, 14: 67, 1944.
 38. BEAMS, A. J. The treatment of cirrhosis of the liver with choline and cystine. *J. A. M. A.*, 130: 190, 1946.
 39. STEIGMANN, F. The efficacy of lipotropic substances in the treatment of liver cirrhosis. *J. A. M. A.*, 137: 239, 1948.
 40. BEST, C. H., HERSHEY, J. M. and HUNTSMAN, M. E. The control of the deposition of liver fat. *Am. J. Physiol.*, 101: 7, 1932.
 41. MILLER, L. S., ROSS, J. F. and WHIPPLE, G. H. Methionine and cystine, specific protein factors preventing chloroform liver injury in protein depleted dogs. *Am. J. M. Sc.*, 200: 739, 1940.
 42. GILLMAN, T. and GILLMAN, J. Powdered stomach in the treatment of fatty livers and other manifestations of infantile pellagra. *Arch. Int. Med.*, 76: 63, 1945.
 43. FRANKLIN, M., SALK, M. F., POPPER, H. and STEIGMANN, F. Clinical, functional and histologic responses of fatty metamorphosis of human liver to lipotropic therapy. *Am. J. Clin. Path.*, 18: 273, 1948.
 44. BARKER, M. H., CAPPS, R. B. and ALLEN, F. W. Chronic hepatitis in the Mediterranean theater—a new clinical syndrome. *J. A. M. A.*, 129: 653, 1945.
 45. JONES, M. C. and VOLWILER, W. Therapeutic consideration in subacute and chronic hepatitis. *M. Clin. North America*, 1059, September, 1947.

The Correlation of Hepatic Structure and Function*

LAURANCE W. KINSELL, M.D., HARRY A. WEISS, LT. (MC) U.S.N., GEORGE D. MICHAELS, PH.D., JOHN S. SHAVER, COMDR. (MC) U.S.N. and HARRY C. BARTON, JR., LT. (MC) U.S.N.

Oakland, California

THE wave of enthusiasm for the performance of liver biopsy as a routine diagnostic procedure dates from the demonstration by Iverson and Roholm¹ that the technic is simple, relatively safe when carried out with proper attention to detail and provides a piece of liver tissue of sufficient size to permit of serious histologic study. Hoffbauer² published an excellent review of the evolution of the procedure to date in which he considers the advantages and disadvantages of various technics. He believes, as we do, that the Vim-Silverman needle technic, as originally described by Tenopyr and Silverman³ and by Tripoli and Fader,⁴ is safe and efficient. All specimens considered in this study were obtained by this method. Only an anterior approach has been used and biopsy has been limited to patients with palpable livers. In the course of more than a hundred such biopsies no mishaps have occurred.

Histologic evaluation of these specimens in this clinic constitutes one part of a broad program of investigation of the normal and abnormal clinical physiology of the liver. In this report we shall attempt to correlate biopsy, clinical and biochemical findings in selected patients studied under controlled conditions. In attempting such correlation we have indulged in purposeful oversimplification of an extremely complex problem.

CLINICAL MATERIAL

A large group of patients with acute, subacute and chronic liver disease has been followed clinically, chemically and histologically over prolonged periods of time. The acute group has included individuals with all degrees of severity of "epidemic viral" and "homologous serum" hepatitis. Of those men with subacute (obviously a relative term) forms of hepatic involvement the majority have represented cases of non-resolving viral hepatitis but at least two men have had long-continued cholangitis referable to coccal and/or bacillary infection.

The patients with chronic liver disease, i.e., "cirrhosis," have had, with only one exception, a history of use and abuse of alcohol over fifteen or more years. The majority have been in the fourth decade.

For the purposes of this report three acute, one subacute and five chronic patients have been arbitrarily selected from the larger group as being most carefully studied and most representative.

STUDIES

Clinical Criteria. In the clinical evaluation of these patients, certain objective entities have been carefully recorded for comparative purposes: (1) general nutrition; (2) apparent degree of scleral icterus;

* From the Division of Medicine, University of California Medical School, and Department of Medicine, U. S. Naval Hospital, San Francisco and Oakland, California.

This work is supported by grants from the Research Division of the Bureau of Medicine and Surgery, U. S. Navy (BuMed #007046), and from the Office of Naval Research under a contract between the latter and the University of California. This paper was presented in part at a regional meeting of the American Federation for Clinical Research on November 6, 1947, held in San Francisco.

(3) liver size, as noted at the right anterior axillary line (cm. below the rib margin); (4) degree of splenomegaly, if present; (5) venous dilation—chest, abdomen and back; (6) spider angiomas; (7) degree of ascites, if present; (8) degree of dependent edema, if present; (9) evidence of "vitamin B deficiency" as manifested by abnormalities of the tongue, skin and mucous membranes; (10) status of appetite, particularly in relation to therapy; (11) gynecomastia, if present; (12) fetor hepatis if present. In the text gradation of positive physical findings are arbitrarily recorded on a 1+ to 4+ basis.

Histology. Initially the entire specimen obtained from the Vim-Silverman needle—a cylinder of tissue 2 mm. in diameter and varying from 1 to 3 cm. in length in the fresh state—was fixed in formalin and stained with hematoxylin and eosin. As our technic improved and the usual specimen approached the 3 rather than the 1 cm. length the tissue was divided, half being placed in formalin and half in absolute alcohol for later staining with Best's carmine. Other stains, including osmic acid, Sudan III and prussian blue (for iron pigment), have also been used. With few exceptions, as will be noted below, the hematoxylin and eosin, and carmine preparations gave us as much or more information than we were able to obtain with other technics.

Chemistry. In an organ such as the liver with (normally) such homogeneity of cellular structure and such extreme multiplicity of chemical activities, it would at first glance seem almost a hopeless task to set up any system of chemical evaluation which could be correlated well with structural alteration.

In our chemical panel we have attempted to include quantitative or semi-quantitative procedures which would give some information concerning: (1) the excretory-detoxification mechanisms (icterus index, free and combined bilirubin blood levels, bromsulfalein removal and hippuric acid excretion); (2) protein metabolic activities (serum albumin and globulin; NPN; urea

nitrogen; plasma amino acid nitrogen and uric acid nitrogen; and methionine utilization); (3) carbohydrate metabolism (glycogen storage test); (4) fat and steroid metabolism (serum free and esterified cholesterol; metabolism of administered androgen, as manifested by 17-ketosteroid excretion); (5) certain tests dependent upon aberrations of serum globulin and lipoglobulin (prothrombin time; cephalin cholesterol flocculation; thymol turbidity; and sedimentation rate). Only a few of these are emphasized in this phase of the study (*vide infra*).

Scheme of Evaluation. As clinical, histologic and chemical data accumulated we found it necessary to reduce our system to the simplest possible terms if we were to find any basis for correlation.

The textbook description of the liver is that of a great organ comprised of multiple, tiny functional units, these units being so designed that blood from the portal system, containing the products of intestinal digestion, is mixed with highly oxygenated blood from the hepatic artery just before its passage between the rows of hepatic cells in the anatomic lobule. During this passage, through the joint activity of the Kupffer cells and the liver cells, certain metabolites are removed from and others added to the stream which then rejoins the general circulation by way of the hepatic vein. The normal histologic structure and functions of such a lobule are shown schematically in Figure 1.

In arriving at a system of histologic evaluation, we initially searched for any abnormality or series of abnormalities in liver cells *per se* which would show consistent correlation with specific clinical or chemical findings. To date no such specific correlation has been found; hence we still find it necessary to speak of "gross hepatocellular change, as manifested by aberration in size and shape of liver cells, by widespread multinucleation, and by abnormal staining characteristics." Aside from such complex hepatocellular pathology, study of any considerable number of biopsy sections focuses one's attention upon the relative amount of

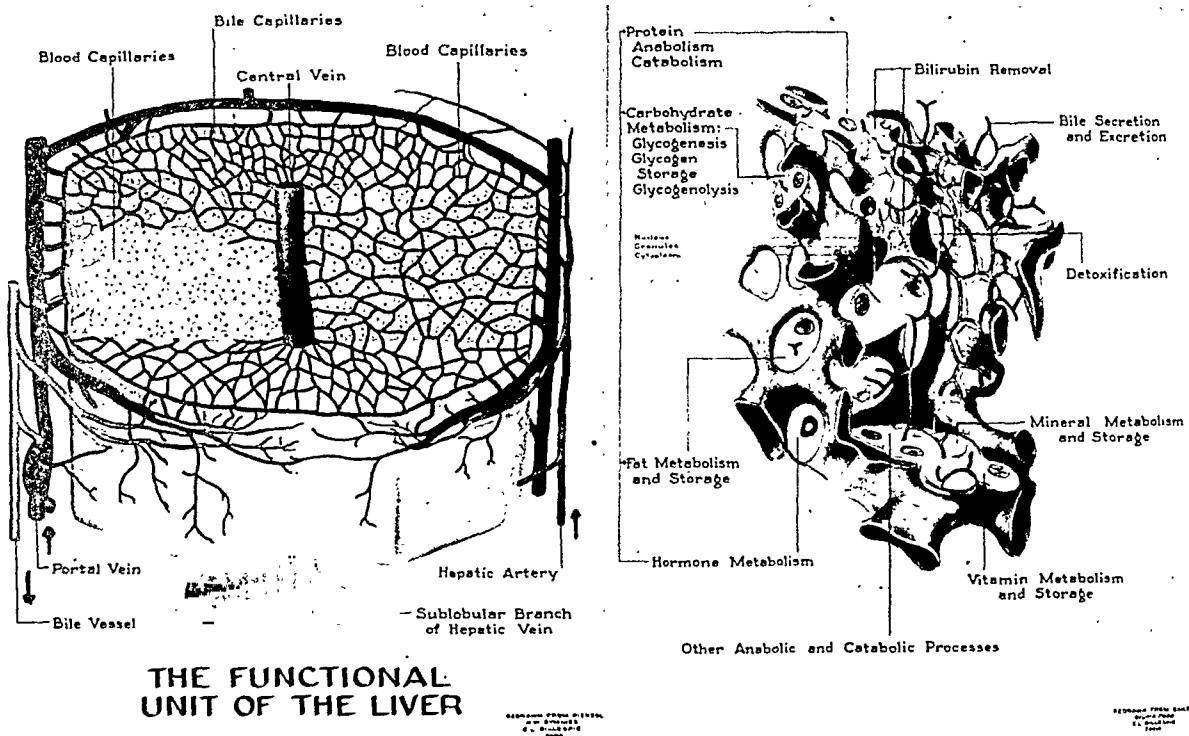


Fig. 1. Schematic presentation of structure and function of the hepatic lobule. (Courtesy of authors and publisher.)

connective tissue present and upon the amount and kind of cellular and non-cellular infiltrations found within and between lobules. Histologic evaluation of this sort followed by correlation of the biopsy sections with clinical and chemical findings resulted in the establishment of the following concept for evaluation and correlation:

$$\begin{array}{l} \text{Dietary} \qquad \qquad \text{Toxic Agent} \\ \text{Insufficiency} \quad + \quad (\text{Infectious or Chemical}) \\ \qquad \qquad \qquad = \text{Hepatocellular} + \text{Phagocytic} \\ \qquad \qquad \qquad \qquad \text{Damage} \qquad \qquad \text{Infiltration} \end{array}$$

Enzymes or other agents produced by damaged liver cells and/or phagocytes result in fibroblastic proliferation.

Interpretation of liver sections, then, may be based upon the following criteria: (1) Cellular infiltration (round cells and other phagocytes) constitutes an index of activity, usually correlated with the cephalin cholesterol flocculation and other similar tests and at times with the serum bilirubin level. (2) Hepatocellular change, as manifested by aberration in size and shape of liver cells, by widespread multinucleation and by ab-

normal staining characteristics, is an index of activity and of extent and severity of the hepatotoxic process. Chemically, it is usually correlated with elevation of serum bilirubin, with bromsulfalein retention and with decreased hepatic glycogen storage. (3) Fibrosis is an index of duration and extent of over-all liver damage. It may be correlated with bromsulfalein and glycogen storage changes but in the presence of otherwise normal hepatic parenchyma may be compatible with normal chemistry.

The obvious defect in such an approach is its superficiality; its virtue lies in the avoidance of controversial material. That it represents only a transitional phase in the concept of the subject is apparent.

Laboratory Methods. All liver function tests and other chemical procedures have been performed by generally accepted and proven procedures.⁵⁻²¹ The Howe sodium sulfate precipitation has been used for globulin precipitation; it is recognized that this may at times give misleading information in patients with liver disease but other methods (electrophoresis excepted) are not yet adequately standardized. Bromsulfalein

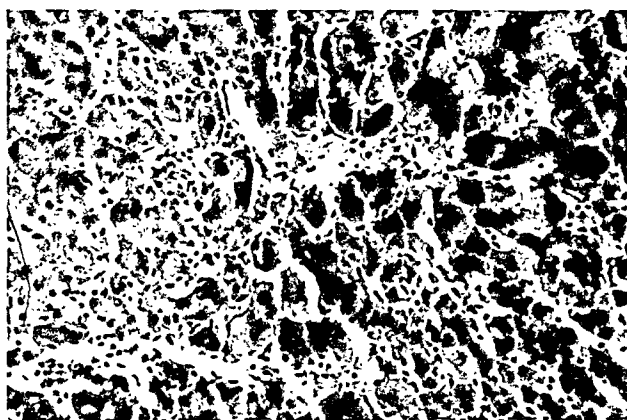
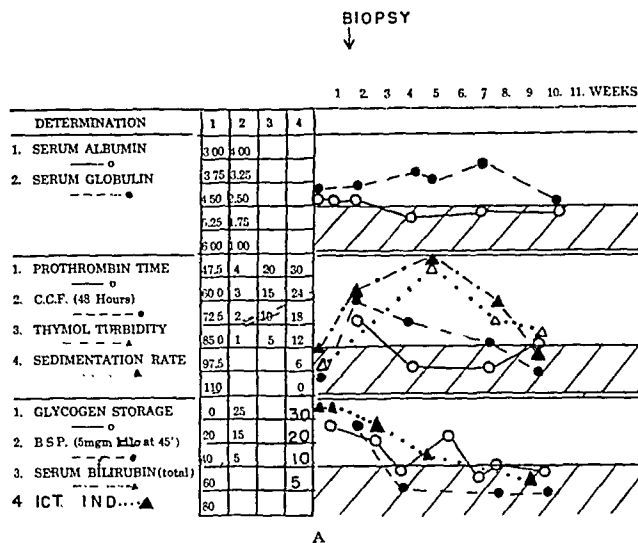


FIG. 2. Case I. A and B, chemical and histologic findings; diagnosis: hepatitis, acute.

colorimetry was performed with the Beckman spectrophotometer.

FINDINGS

CASE I. *Acute Liver Damage.* H. A. U., No. 153350, a male, aged thirty-two, had been ill for five weeks at the time of admission. The onset of his disease was quite typical of acute hepatitis, consisting of a history of malaise followed by the appearance of dark urine, nausea, vomiting, fever and clinical jaundice.

On admission his findings were: nutrition—fair; scleral icterus—3+; liver size—7 cm. in the anterior axillary line; splenomegaly—none; venous dilation—none; spider angiomas—none; ascites—none; dependent edema—none; gross vitamin deficiency—minimal; gynecomastia—none; appetite—poor; fetor hepaticus—none. He represented, then, a patient with a typical viral hepatitis of more than average severity,

showing at the time of admission no tendency to spontaneous resolution.

Biopsy obtained eight days after admission showed: (1) three plus round cell infiltration involving not only the periportal area but all peripheral portions of the lobule; (2) one plus increase in fibroblasts in the portal region; (3) widening of the bile capillaries; (4) the presence of bile thrombi; (5) abnormalities of size, shape and staining quality of the liver cells.

Chemical findings at the time of the initial biopsy included: cephalin cholesterol flocculation, sedimentation rate and prothrombin time—all abnormal immediately preceding the biopsy; thymol turbidity—normal, later becoming abnormal. Strangely enough, both sedimentation rate and cephalin cholesterol flocculation were normal on admission despite the five-week duration of the disease. For this we have no explanation. Hepatic glycogen storage

was markedly diminished; bromsulfalein removal, diminished; and icterus index, 3 + elevated.

EVALUATION:

1. Activity

Histology—marked cellular infiltration—hence marked activity

Chemistry—cephalin flocculation and sedimentation rates abnormal

Correlation—good

2. Extent and Duration

Histology—fibroblastic proliferation—not marked; hepatocellular change—marked

Chemistry—Bromsulfalein removal—diminished; glycogen storage—markedly diminished

INTERPRETATION:

Histology—widespread active process of recent onset

Chemistry—widespread active process, duration unknown

Correlation—good

This man was admitted at the same time as Case II (*vide infra*). Both were placed on a balance study regimen in which they received the equivalent of 115 Gm. of protein as casein hydrolysate intravenously in addition to other essential dietary constituents. On this program the patient improved clinically and chemically and his liver receded under the costal margin within two weeks so that a second section was not obtained. The rapid resolution under adequate therapy would suggest a relatively recent process and hence would make for even better correlation. The histologic and chemical findings are shown in Figure 2.

CASE II. J. O. N., No. 153359, a male, aged twenty, had been ill for three weeks at the time of admission. His past history was possibly of significance inasmuch as he had had an attack of jaundice some years previously and had recently had a chancre for which he had been treated with arsenic, bismuth and penicillin.

The onset of his present illness was classical for viral hepatitis. With the exception of a somewhat more intense icterus, higher fever and more marked hepatomegaly, his pertinent clinical findings on admission were identical with those in Case I. Their general clinical similarity and the severity of the disease process caused us to select them for a balance study which will be described elsewhere.

Liver biopsy was obtained immediately following admission and again seven weeks later. These biopsies showed: (1) intense round cell infiltration, less apparent in the seven-week biopsy but still definitely present; (2) fibrosis of sufficient degree to make the concept of pre-existing liver damage mandatory; (3) widening of bile capillaries; (4) the presence of bile thrombi; and (5) extreme alterations of normal hepatocellular structure, namely, abnormal staining characteristics, multinucleation and gross variation in cell architecture. The seven-week biopsy showed essential disappearance of (3), (4) and (5) but persistence of (1) and (2).

At the time of the first biopsy all tests were abnormal chemically with the exception of thymol turbidity. Seven weeks later (third biopsy) the bromsulfalein and glycogen storage tests had reverted to normal as had also the cephalin cholesterol flocculation. The sedimentation rate continued high although less so, and the thymol turbidity had become abnormal. The histologic and chemical findings are shown in Figure 3.

EVALUATION:

1. Activity

Histology—round cell infiltration throughout, as well as major hepatocellular abnormality

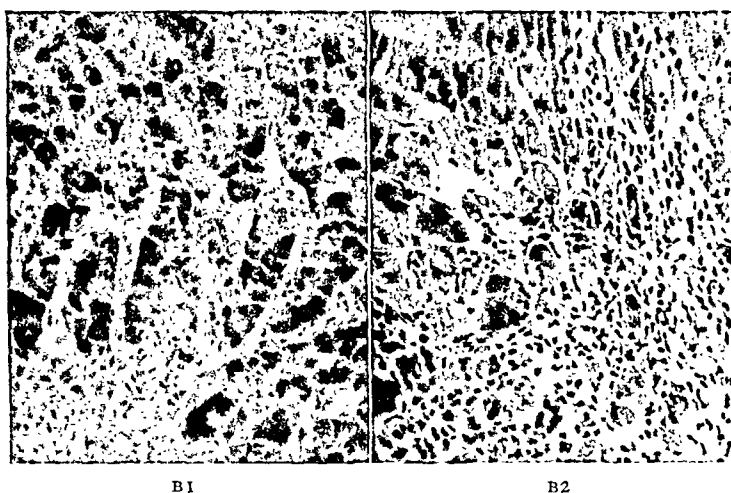
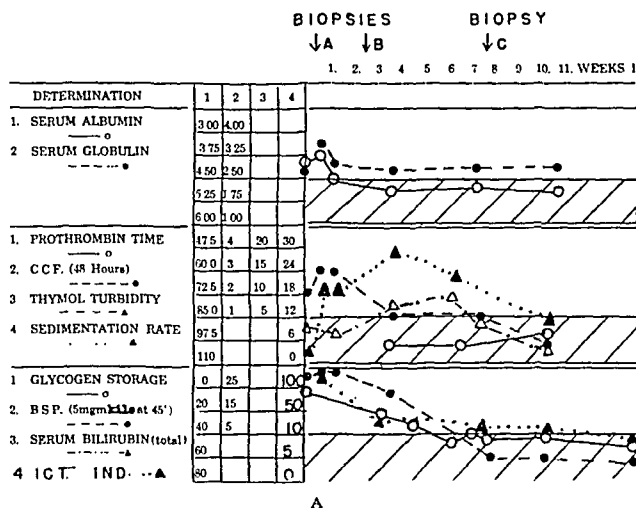
Chemistry—all tests initially abnormal; at the time of the seven-week biopsy the thymol turbidity test and the sedimentation rate were the only remaining abnormal chemical findings

Correlation—good, if one uses both cephalin cholesterol flocculation and thymol turbidity. The cephalin cholesterol flocculation alone would be misleading as an index of activity in late convalescence (*vide infra*)

2. Extent and Duration

Histology—initial, (B1) fibroblastic proliferation 2+, hepatocellular change 3+: final, (B2) fibroblastic proliferation 2+; hepatocellular change, nearly normal

Chemistry—bromsulfalein and glycogen storage, both initially abnormal, had reverted to normal limits at the time of the seven-week biopsy



B1

B2

FIG. 3. Case II. A and B, chemical and histologic findings; diagnosis: hepatitis, acute; (B1) initial biopsy; (B2) final biopsy.

INTERPRETATION:

Histology—widespread severe, acute process, superimposed upon pre-existing liver damage

Chemistry—widespread, active process, duration unknown

Correlation—good

This man's further progress was satisfactory and he was subsequently discharged from the hospital clinically and chemically well but with a liver undoubtedly badly scarred and probably vulnerable to exposure to noxious agents.

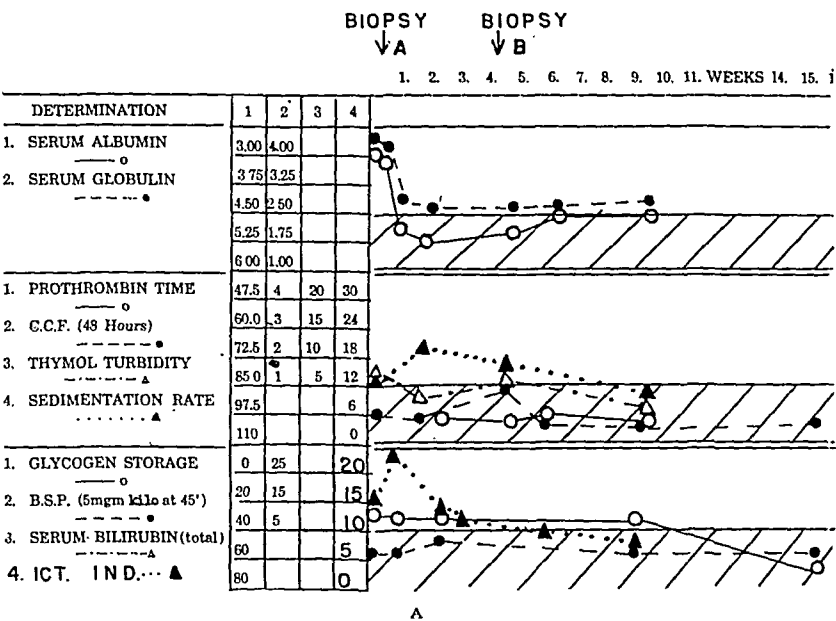
CASE III. W. I. N., No. 153579, a male, aged twenty-six, was admitted with a history of a typical onset of acute viral hepatitis two months previously. He had been on a partial regimen of bed rest elsewhere before admission to this hospital. On admission here he still had moderate clinical icterus which had almost disappeared at the time of the first biopsy two weeks later.

Except for hepatomegaly, moderate anorexia and some weakness, he was free of symptoms and signs at the time of the first biopsy. At the time of the second biopsy three weeks later he showed steady clinical improvement and decreasing hepatomegaly.

The histologic findings were: initial, (B1) round cell infiltration 2+; hepatocellular changes, minimal; fibrosis 1+; three weeks later, (B2) almost normal liver architecture.

The chemical findings at the time of initial biopsy were: cephalin cholesterol flocculation, normal; thymol turbidity and sedimentation rate, moderately abnormal; bromsulfalein, normal; and glycogen storage, moderately decreased; at the time of second biopsy, all findings were normal except the glycogen storage test. The histological and chemical findings are shown in Figure 4.

As in Case II the best correlation in terms of acuteness is noted between the thymol turbidity



A

B1

B2

FIG. 4. Case III. A and B, chemical and histologic findings in patient W.I.N.; diagnosis: hepatitis, acute. (B1) initial biopsy; (B2) final biopsy.

and the round cell infiltration. The normal cephalin cholesterol flocculation is probably referable to the length of time elapsing since the onset of the disease.

The abnormal glycogen storage is not correlated with any demonstrable histologic abnormality in the second biopsy section. That this man had significant hepatomegaly long after all other liver function tests had become normal, and that his glycogen storage did eventually reach normal levels at about the time his hepatomegaly disappeared are of interest.

The general correlation was fair. His subsequent course was eventually that of thorough convalescence, namely, about seven months after the onset of the disease.

CASE IV. *Hepatitis, Chronic.* C. U. M., No. 149147, a male, aged twenty-six, was admitted for study approximately six months after the onset of an attack of acute hepatitis which had apparently been quite severe. Clinical jaundice was said to have persisted for four months. Spider angiomas appeared five weeks after the onset of the disease and were present throughout his period of observation in this hospital. He gave a history of jaundice ten years previously.

On admission, his findings were: general nutrition—fair-poor; scleral icterus—1+; liver size (AAL)—4 cm., quite hard; spleen—±; venous dilation—0; spider angiomas—2+; ascites—0; dependent edema—0; “B” deficiency—moderately red tongue; appetite—poor; gynecomastia—0; “feter”—present.

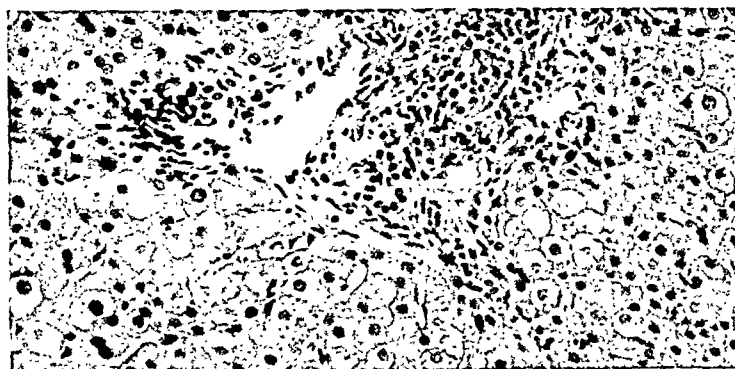
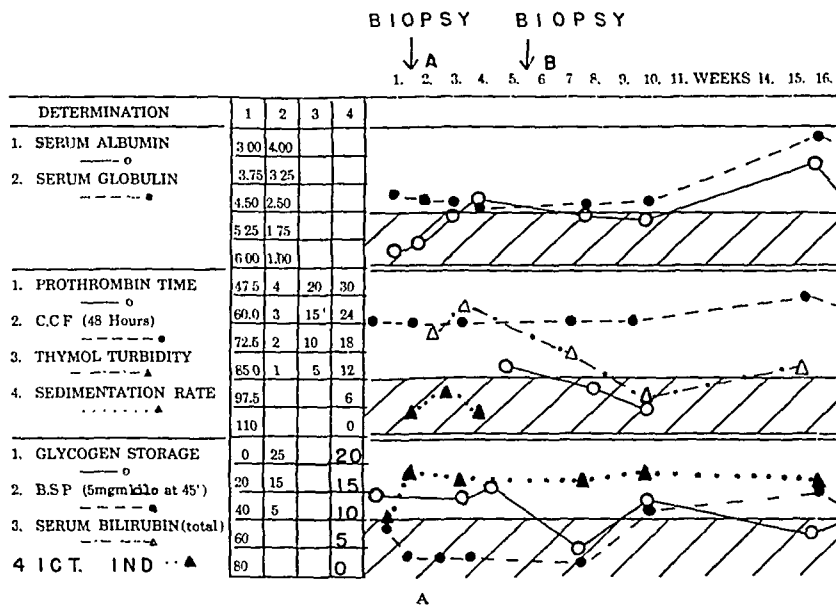


FIG. 5. Case iv. A and B, chemical and histologic findings in patient C.U.M.; diagnosis: hepatitis, chronic (viral).

Biopsy was performed on several occasions but was productive of only one good specimen, perhaps because of widespread fibrosis. The section shown was obtained just before the beginning of the chemical study. (Fig. 5.) The findings were (1) cellular infiltration, 1+; (2) fibrosis, 1+; and (3) hepatocellular abnormality, 2+.

The chemical findings were: cephalin cholesterol flocculation, abnormal throughout; thymol turbidity, abnormal during most of study; sedimentation rate, normal; glycogen storage, decreased; bromsulfalein, normal at time of biopsy, intermittently abnormal thereafter, over many months.

INTERPRETATION:

Histology—hepatocellular abnormality was the most striking feature in the section obtained; it is highly probable that this man has a much greater degree of gen-

eralized replacement fibrosis than is shown in this section, however

Chemistry—the continued abnormality of the cephalin cholesterol flocculation and glycogen storage are compatible with a concept of continued activity and with a process which is widespread in its involvement

Correlation—fair, in spite of the lack of much cellular infiltration; continuing low grade hepatocellular damage from some toxin, insufficient at this state to excite a marked phagocytic response would appear to be a reasonable explanation

Progress—at this writing, eight months after admission and fourteen months after the onset of this disease, he is still abnormal clinically, chemically and histologically, despite rest, diet and lipotropic agents

Chronic Liver Damage. Five patients are presented under this heading. These five

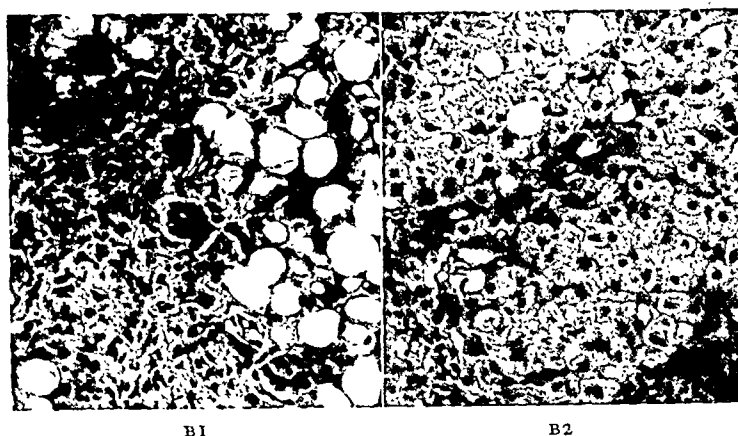
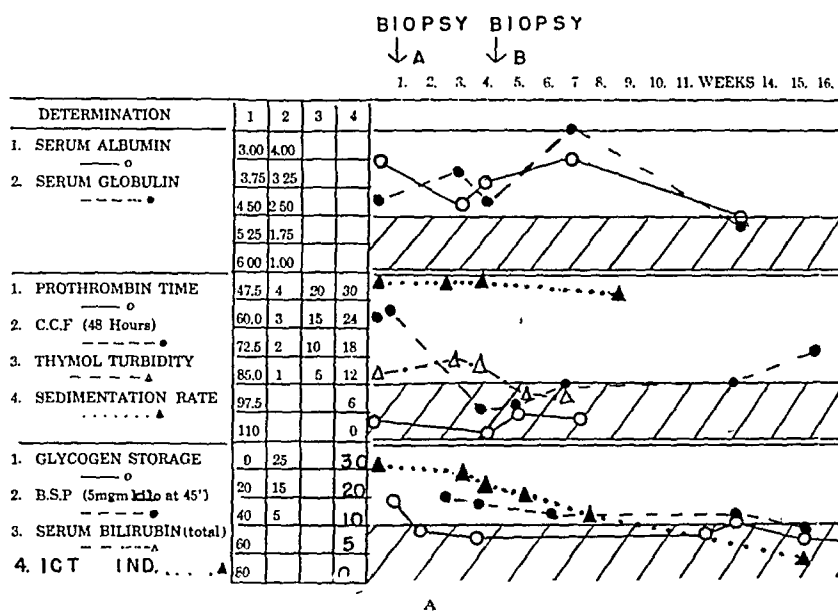


FIG. 6. Case V. A and B, chemical and histologic findings in patient B.E.A.; diagnosis: "cirrhosis"; (B1) initial biopsy; (B2) final biopsy.

are perhaps "representative" of the entire group of "cirrhotics" who have come to us for study and treatment. All five have one factor in common—chronic alcoholism. All have been "spree drinkers" and hence have undoubtedly had periods of significant dietary insufficiency. All had ascites on admission. All but one on "adequate" therapy lost his ascites in a relatively short period of time. All but one has been or will be discharged in reasonably good clinical condition.

CASE V. B. E. A., No. S47-509, forty-three year old, heavy set male, was admitted in near coma, deeply jaundiced, dyspneic and edematous. Aside from his alcoholism extending over a twenty-year period, he has had rheumatic fever with cardiac damage, a previous attack of

jaundice fourteen years ago and lues in 1936 treated with arsenic and bismuth. Acute alcoholism probably precipitated his present episode.

Examination showed: general nutrition—fair; scleral icterus—3+; liver size (AAL)—12 cm., hard; spleen—just palpable; venous dilation—plus 1; spider angiomas—1+; ascites—plus 1; dependent edema—2+; "B" deficiency 2+; appetite—very poor on admission; gynecomastia—none; fetor—present.

Biopsy was performed the day following admission (B1) and again twenty-six days later, (B2) at which time his liver extended only 2 to 3 cm. below the rib margin and he was clinically symptom-free. Therapy during this period had consisted of high protein intake, digitalis and lipotropic agents. Histologic and chemical findings are shown in Figure 6.

The histological evaluation initially, in line with the proposed scheme for evaluation, was: (1) round cell infiltration—3+, hence marked activity; (2) fibrosis—3+, hence widespread, pre-existing damage; (3) hepatocellular change—3+, hence a widespread, active lesion; (4) fatty infiltration—3+; in view of the variety of physiologic processes which can produce this picture, its significance is by no means clear (*vide infra*). Finally, the rapid reversion toward the normal in less than four weeks was most striking. Only fibrosis, slight phagocytic cell and moderate fatty infiltration remained.

Chemically the picture was that of abnormality of all liver function tests studied, all reverting to normal in the space of three weeks. Correlation was excellent.

The rate of improvement in this man must represent a liver still possessing marked regenerative capacity, despite the histologic evidence of widespread fibrosis. The patient was discharged essentially clinically and chemically well about four and one-half months after admission. We understand that he died some weeks later in acute congestive failure in the course of another alcoholic debauch.

The last four men to be described have more factors in common than at variance. To avoid tiresome repetition, we shall present a composite picture of the four and then stress the factors of fundamental importance to this study in which they differ.

The common factors were: (1) age—all but one (W. R. I.—aged thirty-five) were between forty and fifty years of age; (2) alcoholism of more than fifteen years' duration; (3) ascites—present in all on admission; all but one (D. R. E.) had lost his ascites on standard therapy prior to the beginning of this study; (4) hepatomegaly—moderate to marked.

CASE VI. D. R., E., No. 139977. A clinical description of this man must with any propriety include a brief mention of his personal characteristics. We found him over a period of eighteen months to be everything an ex-chronic alcoholic should not be—lovable, dependable, a booster to the morale of the entire ward.

On entry he possessed a huge bulging belly which, superimposed on his long, gangling frame, produced a somewhat Puckish impression. At one time or another he received every

therapeutic agent which has been proven or suspected to be of value in cirrhosis, with little effect. During the last five months of his life (he finally died from a ruptured esophageal varix) he probably received more serum albumin than anyone in history. Despite its failure to do more than delay the inevitable, we count each cubic centimeter well spent. He is described in considerable detail in a paper dealing with protein balance studies. Since he was our first biopsy patient and has just left us as this paper nears completion, we wish to erect a small verbal monument to a friend.

The clinical findings, in addition to those already described, showed splenomegaly—2+; peripheral varicosities—3+; dependent edema—1-3+; fetor—3+ and spiders—3+.

His liver edge and surface were grossly irregular, hard and retracted from the abdominal wall, making biopsy difficult and potentially hazardous. One biopsy was obtained three months before the intensive chemical study was begun. A later biopsy attempt was unsuccessful. The histologic and chemical findings are shown in Figure 7.

The histologic section was obtained three months before the intensive chemical study was begun. On the basis of autopsy findings it is undoubtedly representative of the patient's hepatic histology at any time during the study. The findings were: (1) round cell infiltration—3+, hence marked activity; (2) fibrosis—4+, hence long duration and widespread involvement; (3) hepatocellular change—3+, hence generalized, active involvement.

At no time in the chemical study was any liver function test, except the prothrombin time, even close to normal. The histochemical correlation then, in our crude sense, may be said to be excellent.

CASE VII. D. A. N., No. 15447. Together with the other two men still to be described, this patient is representative of patients with severe liver disease, progressing over many years but still reversible, at least to a degree compatible with fairly normal activity.

Clinically, he showed every textbook finding of advanced cirrhosis, including considerable splenomegaly. Two months after admission he was free of ascites and dependent edema. On his departure some months later, precipitated (against advice) by domestic difficulties, he was clinically vastly improved with almost no remaining hepatomegaly although chemically

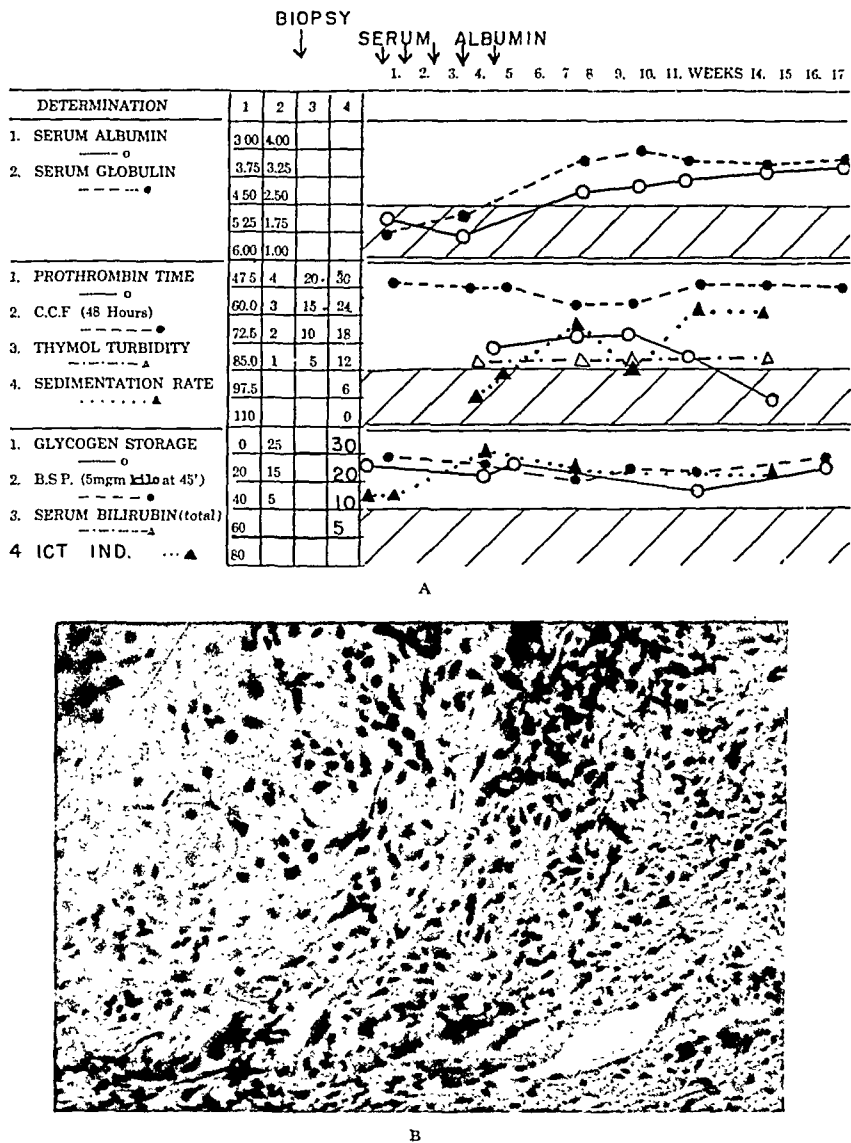


FIG. 7. Case vi. A and B, chemical and histologic findings in patient D.R.E.; diagnosis: "cirrhosis."

still far from well. His letters inform us that he has steered completely clear of alcohol and is doing a full days' work with no difficulty. The histologic and chemical findings are shown in Figure 8.

Biopsies obtained early in the study (but after the disappearance of ascites) (B1) and again a month later (B2) showed little change. Activity: Moderate phagocytic cell infiltration; considerable hepatocellular change. The tremendous amount of fibrosis with choking off of tiny islands of distorted liver cells speak for the widespread damage of long duration.

At no time during the four-month period of intensive chemical study were any normal liver function tests noted, either those which are related to activity or those which are indicative

of widespread damage although the glycogen storage test became less abnormal.

We do not know what the prognosis in terms of life expectancy may be in this man. He is returning to us in the near future for a brief check of his chemical panel. If the findings have reverted to normal his outlook should be good, if he still shows evidence of continued activity, our prognostic outlook will veer in a pessimistic direction. If he has reverted to normal on a program of full activity, we shall question the soundness of the concept of the need for prolonged bed rest in convalescent but not quiescent "cirrhotics."*

CASE VIII. P. A. R., No. 151189, a male, in
* Chemical re-evaluation nine months after discharge showed improvement in all tests.

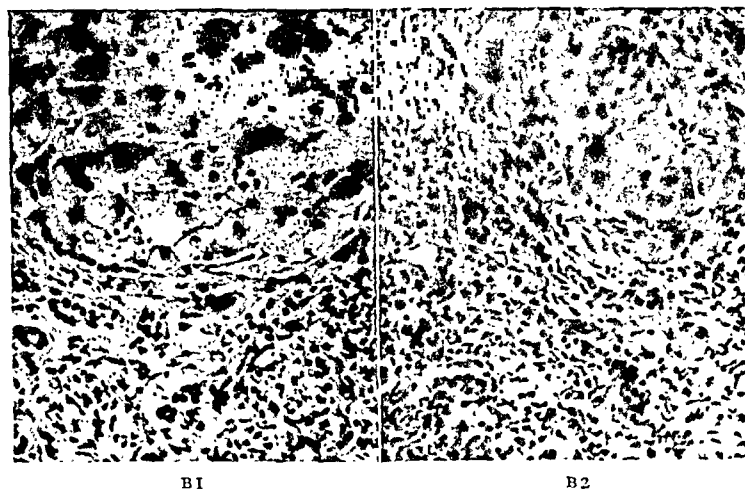
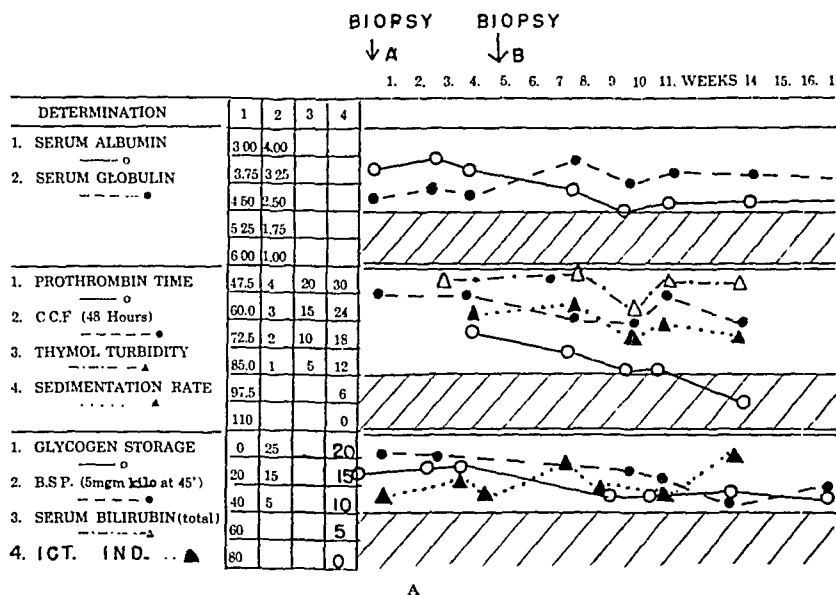


FIG. 8. Case VII. A and B, chemical and histologic findings in patient D.A.N.; diagnosis: "cirrhosis"; (B1) and (B2) are biopsies one month apart.

addition to chronic ethanol addiction had lues some twenty odd years previously and was treated with fairly large amounts of arsenic and heavy metals without incident. His general clinical status was essentially identical on admission with that of Case VII. His chemical response to therapy was even better than that of D. A. N., despite occasional alcohol imbibition. The histologic and chemical findings are shown in Figure 9.

Widespread fibrosis was apparent in both sections. The second section, obtained six to seven weeks after the first during which time impressive clinical improvement had occurred, showed less phagocytic cell infiltration and more normal appearing liver cells. The evaluation was: widespread chronic liver damage (fibrosis)

and decreasing activity of the hepatotoxic process.

The continued abnormality of all liver function tests for a four-month period followed by a gradual decline of the bromsulfalein and glycogen storage test toward normal is the most impressive part of the picture. Resumption of alcohol abuse occurred in the latter part of the study for a considerable time; this may have accounted for the continued abnormality of the cephalin cholesterol flocculation test.

The interpretation was an hepatotoxic process, widespread in extent, but of decreasing intensity; correlation (histology and chemistry) fair. The histology fails to account for the continued abnormal cephalin cholesterol flocculation.

CASE IX. W. R. I., No. 150443, a male, is

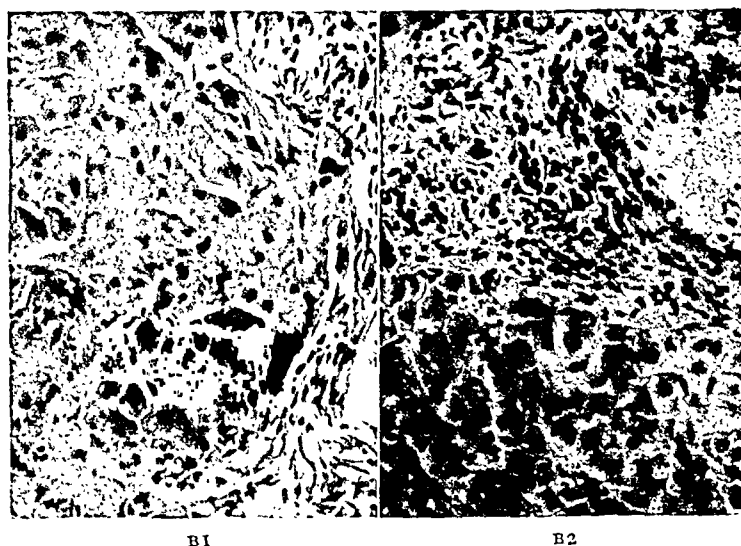
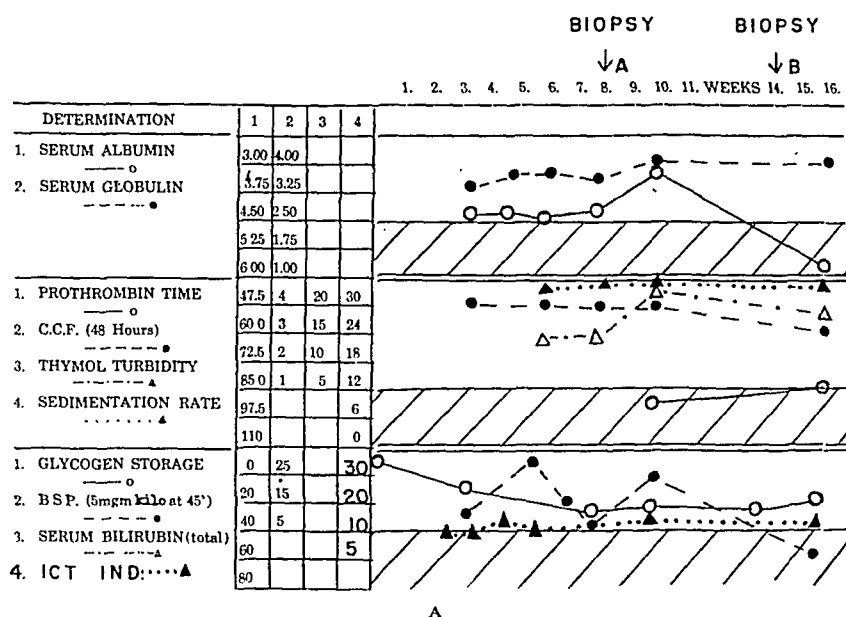


FIG. 9. Case VIII. A and B, histologic and chemical findings in patient P.A.R.: diagnosis: "cirrhosis"; (B1) and (B2) are biopsies six weeks apart.

noteworthy only in that, in contrast to the majority of patients studied, he showed complete lack of correlation between histology and chemistry. Clinically, he was the youngest of all cirrhotics included in this report (thirty-five years), showed the best nutrition, and minimal ascites. The histologic and chemical findings are shown in Figure 10.

Histologically, there was marked fibrosis, round cell infiltration, some in connective tissue, but not in parenchyma and slight hepatocellular change. The impression was that of moderate activity in the presence of widespread liver damage of prolonged duration.

There were normal findings throughout chemically except for transient decrease in glyco-

gen storage following an alcoholic debauch. Obviously the chemical findings would be compatible with the concept of a normal liver. Correlation was very bad; for this we have no explanation at the present time.

This man became quite normal clinically in the space of two to three months. Even the alcoholic episode (which occurred while he was on leave) did not cause his liver to become palpable again.

Consideration of hepatic structure and function, together or singly, could extend interminably. We shall confine ourselves to a few comments on certain points raised by this work.

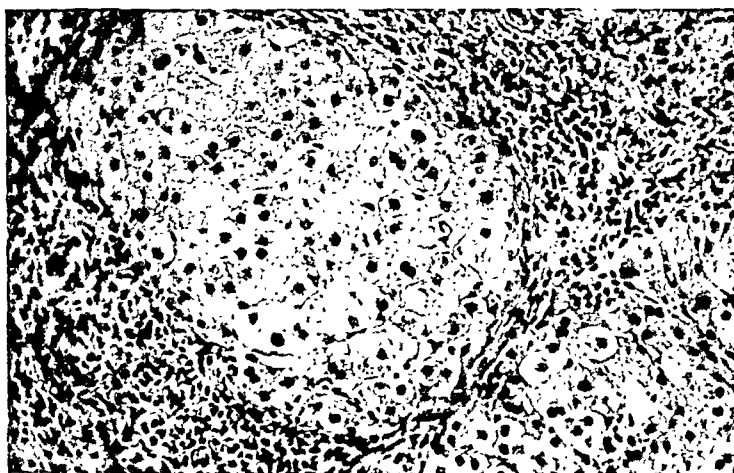
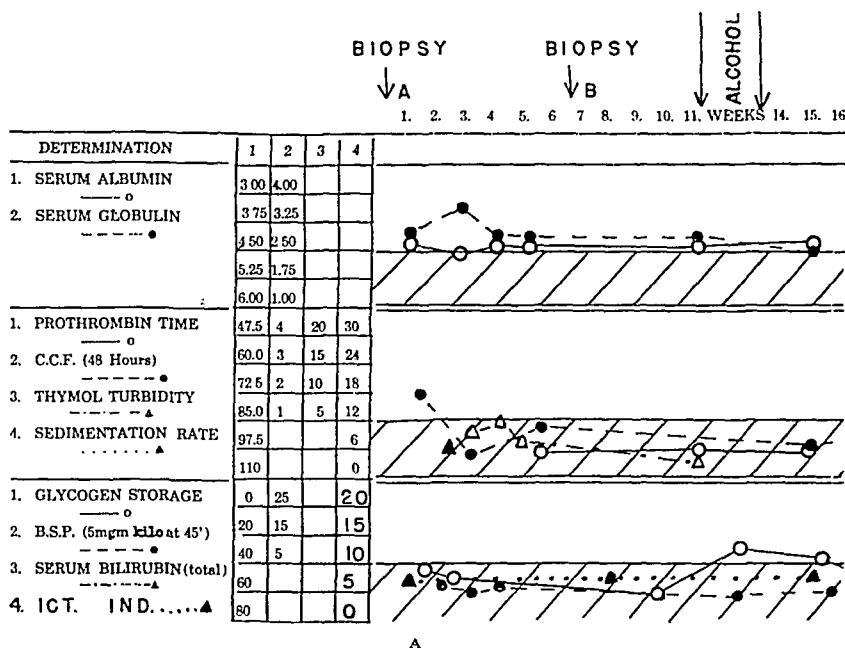


FIG. 10. Case IX. A and B, chemical and histologic findings in patient W.R.I.; diagnosis: "cirrhosis."

CLASSIFICATION OF HEPATIC DISEASE

Chronic Liver Damage. Retention of the term "cirrhosis" in any evaluation of the pathology or physiology of the liver would seem to have little to recommend it. Laennec first used the term in 1826 to describe the color of the liver in autopsy specimens characterized by extensive fibrosis and distortion.²² The later addition to medical nomenclature of the term "hypertrophic biliary cirrhosis" to identify an alleged entity supposedly separate and distinct from Laennec's "atrophic portal cirrhosis" has served only to confuse genera-

tions of medical students and practitioners. It would seem to us probable that many concepts of the pathogenesis, pathology and pathologic physiology of liver disease will rise and fall before the final correct answer emerges.

As one step in this evolutionary process the following may be in order: (1) complete and permanent abandonment of the term "cirrhosis" except in a historical sense; (2) complete abandonment of the concept of "portal" and "biliary" forms of liver disease in the time-honored sense; fibrosis, "biliary obstruction" and hepatocellular

damage are present in all cases; (3) reclassification on a simple, essentially unitarian basis, perhaps somewhat after the fashion previously noted; in any event, a classification which includes the concept of:

A toxin, endogenous or exogenous, acting upon hepatic cells made vulnerable by specific nutritional deficiency resulting in hepatocellular damage with consequent fibrosis of greater or lesser degree.

The rapidity of progression of the damage, its duration and the amount of fibroblastic proliferation would depend on the amount and nature of the toxin and the extent, duration and nature of the underlying nutritional deficiency.

The foregoing concept is based upon a rather vast amount of experimental data originating in many laboratories and extending back over a period of fifteen years, and upon the observations of Patek in 1937 and 1941^{23,24} and of Connor in 1939²⁵ relating to the role of nutritional deficiency in the production of human liver damage. Essentially this concept has formed the basis for the rather remarkably successful therapy now in use in the treatment of patients with liver disease.

Acute Hepatitis. The term "acute hepatitis" is probably both accurate and desirable. Just how variations in the nature of the toxic agent may determine differences in the type of inflammatory reaction, and hence differences in the ultimate histologic picture in the liver, still remains to be shown. Moon adequately summarizes the literature in this field.²⁶ Also to be demonstrated is the role of preceding nutritional deficiency in the production of hepatitis.

Perhaps the final logical nomenclature of liver disease will consist of acute, chronic and healed hepatitis with a modifying adjective referable to the specific etiologic agent.

Fatty Liver. In a previous paper²⁷ we have summarized some of the evidence in the literature relative to the production of fatty livers and of "cirrhotic" livers in animals by dietary means.

Of the patients whom we have presented in this series only one had a significant amount

of fat in the liver parenchyma. Had biopsies been obtained before the institution of therapy in some of the other men it is quite probable that fatty infiltration would have been found. However that may be, it is apparent in this group that severe hepatic parenchymal damage can be present and can progress in the absence of any demonstrable fat deposition.

Conversely, we do not believe that the disappearance of liver fat concurrently with clinical and chemical improvement in such a patient as Case v (Fig. 6) of necessity establishes any significant relationship between liver fat and liver damage. Work currently underway in a number of laboratories may help to further clarify this relationship.

LIVER FUNCTION

The search for better tests of liver function still continues in many laboratories and clinics. For purposes of correlation with structural alteration we have placed the greatest stress on the cephalin-cholesterol flocculation, the bromsulfalein removal, the serum bilirubin and measurement of hepatic glycogen storage.²⁸ This choice is perhaps open to criticism. The inclusion of the thymol turbidity test is probably desirable. It can be said, however, that statistically all four tests show an impressive correlation with the clinical and histologic course of acute and chronic liver disease. That complete lack of correlation with the clinical or histologic findings can occur is well represented in Case ix. (Fig. 10.)

ROLE OF LIVER BIOPSY

In our opinion, the role of liver biopsy may be summarized in a very few words: (1) As a research tool it is justified and valuable. A vast amount of work remains to be done in the evaluation of specific hepatocellular changes. It can serve (2) as a diagnostic tool, when clinical, chemical and roentgenologic findings still leave one in doubt; this applies particularly in the differential diagnosis between non-specific liver damage and tumor. The inability to

be sure that the section obtained is representative of the entire organ is an obvious and serious limitation of the procedure. Moreover, a blind approach to a highly vascular, bile secreting, intraperitoneal organ can never be devoid of risk.

SUMMARY

From study of liver biopsy sections and chemical liver function tests one can only hope for present purposes to obtain rather gross information as to the *activity* of the process which has resulted or is resulting in liver damage, and information as to the *extent and duration* of the process.

Activity is correlated histologically with phagocytic cell infiltration and with hepatocellular change as manifested by widespread multinucleation, abnormalities of cell shape and size, and abnormalities of staining characteristics. The chemical abnormalities which indicate activity are the cephalin cholesterol flocculation and thymol turbidity tests as well as elevation of the serum bilirubin and/or icterus index.

Extent and duration of the hepatotoxic process are manifested histologically by hepatocellular change and by fibrosis. The chemical changes which are found in liver damage of widespread extent and/or long duration are abnormal bromsulphalein retention, diminished hepatic glycogen storage and elevation of the serum bilirubin and/or icterus index.

It is to be emphasized that the above observations are extremely superficial and have nothing to recommend them but their simplicity.

From the foregoing it is evident that our knowledge of liver histology and physiology is in need of many additions; and that when such additional knowledge is obtained, revision of the present archaic classification of liver disease will be in order. An approach to such a reclassification is presented.

Acknowledgment is made to Wyeth, Inc., for supplies of methionine used in the conduct of this work; to Mead Johnson & Co., for supplies of Amigen; and to Eli Lilly & Co. for alpha-tocopherol.

Acknowledgment is made also to Mrs. M. F. Jack for her able assistance in the editing and typing of this and other papers from this laboratory.

REFERENCES

1. IVERSEN, P. and ROHOLM, K. On aspiration biopsy of the liver, with remarks on its diagnostic significance. *Acta med. Scandinav.*, 102: 1-16, 1939.
2. HOFFBAUER, F. W. Needle biopsy of the liver. *J. A. M. A.*, 134: 666-670, 1947.
3. TENOPYR, J. and SILVERMAN, I. The importance of biopsy in tumor diagnosis. *Radiology*, 36: 57-60, 1941.
4. TRIPOLI, C. and FADER, D. The differential diagnosis of certain diseases of the liver by means of punch biopsy. *Am. J. Clin. Path.*, 11: 516-527, 1941.
5. DUCCI, H. and WATSON, C. J. Quantitative determination of serum bilirubin with specific reference to prompt reacting and CHCl_3 -soluble types. *J. Lab. & Clin. Med.*, 30: 293-300, 1945.
6. NEEFE, J. R. and REINHOLD, J. G. Photosensitivity as cause of falsely positive cephalin cholesterol flocculation test. *Science*, 100: 83-85, 1944.
7. BERNHEIM, A. R. Icterus index (a quantitative estimation of bilirubin). *J. A. M. A.*, 82: 291-295, 1927.
8. GAEBLER, O. H. The determination of bromsulphalein in normal, turbid, hemolyzed or icteric serum. *Am. J. Clin. Path.*, 15: 452-455, 1945.
9. POHLE, F. J. and STEWART, J. K. A study of the Quick method for the quantitative determination of prothrombin with suggested modifications. *Am. J. M. Sc.*, 198: 622-630, 1939.
10. SIMMONS, J. S. and GENTZKOW, C. J. Wintrobe tube method for sedimentation rate. *Laboratory Methods of the U. S. Army*. 5th ed., Philadelphia, 1944. Lea & Febiger.
11. NEEFE, J. R. Results of hepatic tests in chronic hepatitis without jaundice (improved thymol turbidity test). *Gastroenterology*, 7: 1-19, 1946.
12. BOYCE, F. F. and MCFETRIDGE, E. M. Studies of hepatic function by the Quick's hippuric acid test. *Arch. Surg.*, 37: 401-426, 1938.
13. FOLIN, O. Standardized methods for determination of uric acid in unlaked blood and in urine. *J. Biol. Chem.*, 101: 111-125, 1933.
14. FRAME, E. G., RUSSELL, J. A. and WILHELM, A. E. Colorimetric estimation of amino nitrogen. *J. Biol. Chem.*, 149: 255-270, 1943.
15. FOLIN, O. System of blood analysis; simplified method for determination of sugar. *J. Biol. Chem.*, 41: 367, 1920.
16. NELSON, N. N. Photometric adaptation of the Somogyi method for the determination of glucose. *J. Biol. Chem.*, 153: 375-380, 1944.
17. HOWE, P. E. The use of sodium sulphate as globulin precipitant in determination of blood proteins. *J. Biol. Chem.*, 49: 93, 1921.
18. KARR, W. G. Method for determination of blood urea nitrogen. *J. Lab. & Clin. Med.*, 9: 329-333, 1924.
19. KOCH, F. C. and McMEEKIN, T. L. A new direct nesslerization micro-Kjeldahl method and a

- modification of the Nessler-Folin reagent for ammonia. *J. Am. Chem. Soc.*, 46: 2066-2069, 1924.
20. KIRK, P. L. A one-piece glass micro-Kjeldahl distillation apparatus. *Indust. & Engin. Chem.*, 8: 223-224, 1936.
 21. KOLMER, J. A. and BOERNER, F. Micro-Kjeldahl method for determination of total protein (and) micro-Kjeldahl method for determination of albumin and globulin. *Approved Laboratory Technic*. 4th ed., New York, 1945. D. Appleton-Century Co.
 22. LAENNEC, R. T. H. *Traité des l'auscultation mediate*. Paris, Schaudé, 2: 196, 1826.
 23. PATEK, A. J., JR. Treatment of alcoholic cirrhosis of the liver with high vitamin therapy. *Proc. Soc. Exper. Biol. & Med.*, 37: 329-330, 1937.
 24. PATEK, A. J., JR. and POST, J. Treatment of cirrhosis of the liver by a nutritious diet, and supplements rich in the vitamin B complex. *J. Clin. Investigation*, 20: 481-505, 1941.
 25. CONNOR, C. L. The etiology and pathogenesis of alcoholic cirrhosis of the liver. *J. A. M. A.*, 112: 387-390, 1939.
 26. MOON, VIRGIL. Experimental cirrhosis in relation to human cirrhosis. *Arch. Path.* 18: 381-424, 1934.
 27. KINSELL, L. W., MICHAELS, G. D., BARTON, H. C. and WEISS, H. A. Protein balance studies in patients with liver damage. II. Effects of lipotropic agents. (In press.)
 28. KINSELL, L. W., MICHAELS, G. D., WEISS, H. A. and BARTON, H. C. Studies in hepatic glycogen storage. I. Adrenalin-induced hyperglycemia as an index of liver function. (In press.)

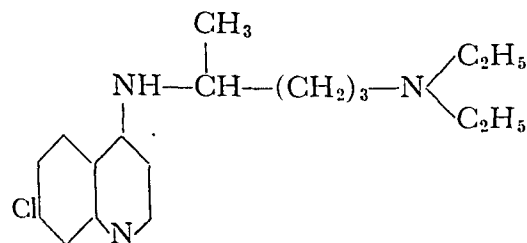
The Treatment of Hepatic Amebiasis with Chloroquine*

NEAL J. CONAN, JR., M.D.†

New York, New York

THE wartime antimalarial drug research program disclosed a number of highly active compounds of the 4-amino-quinoline series. It seemed logical to determine whether their antiplasmodial activity extended to other pathogenic protozoa. The infection selected for study was that with *Endameba histolytica* because of its relative prevalence among protozoal infections in the New York area. Furthermore, although the value of iodohydroxy-quinoline derivatives in the management of intestinal amebiasis had been well established, it had not been determined whether iodine was an essential substituent of the quinoline nucleus for antiamebic activity.

Of the various 4-amino-quinoline derivatives tested for antimalarial activity the greatest amount of information was available concerning chloroquine,^{1,2} 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, which had proven one of the more active and less toxic members of the series.



Chloroquine. 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline

Certain pharmacologic characteristics of this compound made it appear a priori that amebic infections of the liver rather than of the colon would be the test object of

choice. These properties of chloroquine include: (1) its extensive localization in the liver (some five hundred times its plasma concentration) occurring in many animal species and presumably man,² (2) a three- to fourfold lesser degree of localization

TABLE I
AMEBACIDAL ACTIVITY OF VARIOUS DRUGS IN VITRO
AGAINST TROPHOZOITES OF *E. HISTOLYTICA*

Drug	Dilutions of Drugs				Medium
	1/500	1/2000	1/10,000	1/50,000	
Emetine	0 0	0 0	0 0	+ 0	Egg Liver
Chloroquine	0 0	0 0	+ 0	+ 0	Egg Liver
Carbarsone	0 0	+ 0	+ +	+ +	Egg Liver
Anayodin	0 0	± ±	+ +	+ +	Egg Liver

+ = Growth.

0 = No growth.

within the intestinal walls,³ and (3) its almost complete absorption from the gastrointestinal tract,² only some 8 per cent of the daily dose being excreted in the feces, so that the contents of the intestinal lumen, especially the colon, contain a rather small drug concentration.

In vitro studies with trophozoites of *Endameba histolytica* (Table I) conducted by Dr. Harold W. Brown revealed that chloroquine has amebicidal activity supe-

* From the Department of Medicine of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y. An abstract of part of this paper was published in *The Bull. New York Acad. Med.*, 24:545, 1948.

† Now in the Department of Medicine, New York University College of Medicine, New York, N. Y.

rior to that of anayodin and carbarsone but less than that of emetine. Employing a different strain of *E. histolytica*, Dennis⁴ found comparable *in vitro* antiamebic activity of chloroquine. It must be emphasized, however, that extrapolation of *in*

TABLE II
RESULTS OF CHLOROQUINE TREATMENT OF AMEBIASIS

	No. Treated	No. Cured
Intestinal.....	32	17
Hepatic.....	22	22

vitro results to therapeutic activity in human disease may be wholly fallacious. Dennis was unable to demonstrate any activity of chloroquine against natural *Endameba criceti* infections in hamsters.

RESULTS

A preliminary publication⁵ has indicated that chloroquine does possess antiamebic activity in human infections of the liver and colon. So far as intestinal amebiasis is concerned, chloroquine alone has effected symptomatic and parasitologic cure in seventeen of thirty-two cases with follow-up periods of from two to twenty-four months. In regard to hepatic amebiasis the author has now studied seven patients with amebic hepatitis, each of whom was successfully treated with chloroquine. Shookhoff⁶ has confirmed these results in a series of twelve cases of amebic hepatitis. Sodeman⁷ has had comparable results in two cases of acute amebic hepatitis. Murgatroyd^{8,9} has reported the cure of a draining amebic abscess of the liver with chloroquine. Thus twenty-two patients with hepatic amebiasis have now been cured with chloroquine.

The purpose of this publication is to present detailed information concerning the author's seven cases and of Murgatroyd's case which is most informative.

PLAN OF TREATMENT

Oral dosage regimens for testing chloroquine in human amebiasis were devised

with the idea of administering close to the minimal toxic dosage for a period of two to three weeks in order to allow the drug the maximum opportunity for demonstrating *in vivo* antiamebic activity; this resulted in giving, in most instances, a priming or loading dose of 0.6 Gm. of the base for two days in order to saturate the tissues. Plasma and tissue concentrations were then maintained by continuing with a dose of 0.3 Gm. of the base daily for two to three weeks.* Determinations of plasma drug concentrations were not performed in the present study but earlier observations² indicate that they would approximate 176 micrograms per liter.

CASE REPORTS

CASE I. P. H., No. 845126. A fifty-eight-year old white male who had been in China between 1943 and 1945 entered the Presbyterian Hospital in October, 1946. During the eleven weeks prior to admission he had been bothered by two to five loose stools a day associated with crampy, low abdominal pains before and during defecation. He entered the hospital not for this but for an eye operation, following which he developed chills and fever to 104°F. with enlargement and tenderness of the liver accompanied by a leukocytosis of 20,000. X-ray revealed elevation of the right diaphragm and a small right pleural effusion. The cephalin-cholesterol flocculation test was negative. Following demonstration of *Endameba histolytica* in the feces the patient was treated with emetine parenterally, 60 mg. a day for a total of 780 mg., and with chiniofon orally, 3.0 Gm. a day to a total dose of 60.0 Gm. This regimen produced a favorable but only partial effect in that, after a month of treatment, although no amebas could be found in the feces, the patient still had a low grade fever up to 101°F., anorexia, nausea and enlargement and tenderness of the liver. At this

* While the dose of chloroquine has been expressed in terms of the base or active chemical agent, the salt actually used in this study was the diphosphate: 0.15 Gm. of chloroquine base is contained in 0.25 Gm. of chloroquine diphosphate. In terms of the salt then, the dosage schedule employed is 1.0 Gm. of chloroquine diphosphate daily for two days, followed by 0.5 Gm. of chloroquine diphosphate daily for two to three weeks. Chloroquine diphosphate is sold under the name of Aralen diphosphate (Winthrop-Stearns Inc.).

point chloroquine was administered in doses of 0.3 Gm. of the base for thirty-one days. Within a week all symptoms disappeared, the appetite improved followed by a gain in weight and the liver became neither obviously enlarged nor tender. It must be mentioned that during the first week of treatment the patient complained of nausea about one hour after each dose of chloroquine. The nausea, however, disappeared despite continued medication. The patient has remained well for the succeeding twenty-four months.

CASE II. P. H. 852316. A sixty-one-year old male came to the Presbyterian Hospital from El Salvador in December, 1946, complaining of "colitis" of ten years' duration manifested by upper abdominal cramps and two to three loose stools a day, a continuous dull pain in the right upper quadrant of eight months' duration, and for the past six months weakness, anorexia and weight loss. Physical examination revealed a tender liver, which was enlarged to two to three finger-breadths below the right costal margin, and left lower quadrant tenderness. Complete blood count, urinalysis and Kline test were normal. The cephalin-cholesterol flocculation test was negative. Serum alkaline phosphatase was 3.3 Bodansky units per cent (B. U. per cent). At thirty minutes there was 15 per cent bromsulfalein (BSP) retention. Cysts and trophozoites of *Endameba histolytica* were found in the stools. Barium enema revealed evidence of inflammation in the descending and sigmoid colon. A gastrointestinal series was interpreted as showing gastroduodenitis. The cholecystogram was normal. Chloroquine was administered in doses of 0.6 Gm. of the base daily for two days followed by 0.3 Gm. of the base daily for twelve days. On the second day of treatment neither enlargement nor tenderness of the liver could be demonstrated. On the last day of treatment anorexia, nausea and vomiting occurred. This was thought to be due perhaps to the gastroduodenitis rather than to chloroquine since all symptoms promptly cleared following administration of alkali. After treatment four stools were negative for amebas, the BSP test showed only 7 per cent retention and all symptoms had disappeared. The follow-up period is only one and one-half months because at this time the patient returned to El Salvador and has not been heard from since.

CASE III. P. H. No. 862925. A fifty-three-year old white male who had never left the

United States entered the Presbyterian Hospital in March, 1947. The previous medical history included an appendectomy in 1909, typhoid fever in 1911, an undiagnosed illness in 1943 quite similar to the present illness, and a duodenal ulcer with symptoms in 1944 but not since then. Abdominal cramps, diarrhea and constipation were denied. The present illness was of two to three weeks' duration and consisted of persistent high fever, occasional shaking chills, a constant severe epigastric and right upper quadrant pain which radiated to the right shoulder, and a 5 pound weight loss. Physical examination revealed fever, right upper quadrant tenderness and muscle spasm as well as right costovertebral angle percussion tenderness. The white blood count was 17,200, erythrocyte sedimentation rate (ESR) was 122 mm. at one hour, BSP retention at thirty minutes was 12 per cent, and the serum alkaline phosphatase was elevated to 8.2 B.U. per cent. The cephalin-cholesterol flocculation test was negative. The hemoglobin concentration, red blood count, urinalysis, stool culture, various bacterial agglutination tests and the Kline test were normal. Gastrointestinal series revealed a duodenal ulcer. Barium enema showed a deformed contracted cecum, a patent ileocecal valve and a loop of terminal ileum adherent to the cecum. Fluoroscopy demonstrated splinting of the right diaphragm and a small pleural effusion. Cholecystogram was normal. Trophozoites of *Endameba histolytica* were found in the stools and the amebiasis complement fixation test was positive (+++). At the end of the second hospital week, fever and pain had abated somewhat but were still present, as were the diaphragmatic splinting, pleural effusion, ESR of 116 mm. at one hour, elevated phosphatase and the BSP retention. Chloroquine was then given in doses of 0.6 Gm. of the base daily for two days, followed by 0.3 Gm. of the base for nineteen days. (Fig. 1.) On the fourth day of treatment all pain, tenderness and fever had disappeared as had the diaphragmatic splinting and pleural effusion. As treatment continued the ESR fell progressively to 11, the BSP from 12 per cent to 0 per cent retention and the alkaline phosphatase from 8.2 to 4.4 B.U. per cent. The patient regained his appetite, weight and strength. During the third week of chloroquine treatment the stools, which had become negative, again showed amebas which promptly disappeared with administration of chiniofon, 2.25 Gm.

daily for eleven days. The patient has been well for the succeeding twenty-one months during which purged stools every two months have revealed no amebas, the complement fixation test has decreased from +++ to \pm , and the barium enema reveals marked improvement in the cecum.

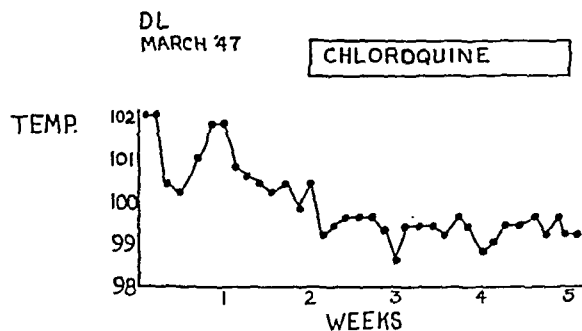


FIG. 1. Temperature chart in Case III. In this and subsequent charts only the maximal daily temperatures are recorded.

CASE IV. V. H., No. 97395. A twenty-five-year old colored male veteran was admitted to the Veterans Administration Hospital in the Bronx in July, 1947, complaining of chills, fever, right upper quadrant pain, cough, anorexia and nausea of four days' duration. During the previous seven months several episodes of nausea had occurred accompanied by abdominal cramps and diarrhea which occasionally had been bloody. The only point of importance in the past history was a thirteen-week hospitalization period with acute infectious hepatitis while in the Philippines. Physical examination revealed fever and an enlarged, tender liver with considerable overlying muscle spasm. Laboratory studies were as follows: blood count normal including a negative test for sickling, urinalysis negative, cephalin-cholesterol flocculation test negative, serum albumin 3.6 Gm. per cent, globulin 2.5 Gm. per cent, alkaline phosphatase 1.6 B.U. per cent and an icterus index of 8. There was 5 per cent retention of BSP at forty-five minutes. Purged stools showed many trophozoites of *Endameba histolytica*. Various bacterial agglutination tests and blood cultures were negative. The amebiasis complement fixation test was + + + +. X-ray of the lungs was normal. Barium enema demonstrated considerable inflammation of the terminal ileum, cecum and ascending colon. For three and one-half weeks the patient received treatment (Fig. 2) for intestinal amebiasis consisting of 2.53 Gm. of diodoquin orally for ten days followed by

1.0 Gm. of carbarsone a day for ten days, the latter being concurrent with retention enemesis containing 8.8 Gm. per cent chiniofon for seven nights. This eliminated parasites from the feces but had no effect upon the hepatitis. At the end of this treatment the liver was still tender and enlarged to 6 cm. below the right costal

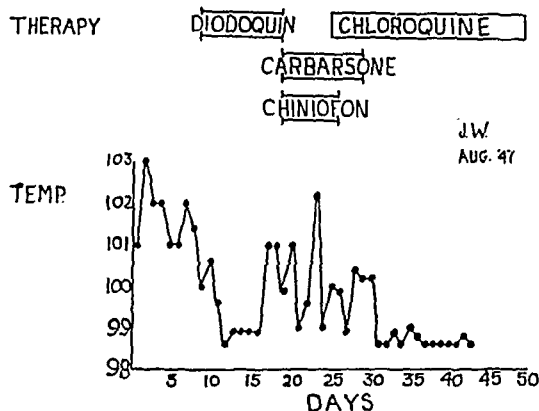


FIG. 2. Temperature chart in Case IV.

margin, a right-sided pleurisy had developed as manifested by pleuritic pain and friction rub accompanied by radiologic evidence of a small pleural effusion. In addition the phosphatase had risen from 1.6 to 6.0 B.U. per cent and the white blood count from 8,400 to 18,000. At this juncture chloroquine was administered in doses of 0.6 Gm. of the base daily for two days followed by 0.3 Gm. of the base daily for nineteen days. On the fourth day of this therapy the liver was only 3 cm. below the costal margin and was much less tender with no overlying muscle spasm. At the same time the white count had dropped from 18,000 to 7,500. On the eighth day of chloroquine treatment the liver was neither palpable nor tender, the phosphatase had dropped from 6.0 to 2.6 B.U. and BSP from 6 per cent retention to no retention in forty-five minutes, the patient had regained his appetite and some of his lost weight and the pleurisy had cleared completely. He has been perfectly well now for fourteen months.

CASE V. P. H., No. 894190. A twenty-six-year old male veteran entered Presbyterian Hospital in December, 1947, complaining of two months of fever up to 104°F. with night sweats and 30 pounds weight loss, as well as three weeks of right upper quadrant pain which radiated to the right shoulder. The whole illness began in November, 1942, in the midwest before the patient ever left the United States. The symptoms then were anorexia and nausea. Two

months later weekly bouts of diarrhea and right lower quadrant pains began for which an appendectomy was performed in April, 1943, without relief of the symptoms which continued intermittently. Early in 1944 a duodenal ulcer was demonstrated by a gastrointestinal x-ray but there was only slight relief on an ulcer diet. Bloody diarrhea first appeared in May, 1944, at which time the patient was hospitalized for six months in an army general hospital where he was told he had colitis, was treated with emetine and discharged from the army in November, 1944. Between this time and November, 1947 the patient suffered from several episodes of cramps and diarrhea. On November 4, 1947, the sudden onset of fever occurred which ranged from 102° to 104°F., chilliness, sweats, anorexia and profound malaise for which the patient received 5,000,000 units of penicillin over a six-day period with a diagnosis of pneumonia. Following this treatment there were two weeks with no symptoms after which the fever and nausea recurred but were now complicated by severe right upper quadrant pain radiating to the back and shoulder. Throughout these two months there were no cramps or diarrhea.

Physical examination disclosed fever of 102°F., splinting of the right diaphragm and a tender liver which extended three finger-breadths below the costal margin. Blood count revealed leukocytosis of 14,000 with a moderate neutrophilia and a slightly low hemoglobin of 12.5 Gm. per cent. The ESR was 60 mm. at one hour. Urinalysis was negative. Eleven stool examinations, most of which followed purges, failed to reveal *Endameba histolytica* or any other parasite. The stool guaiac test was repeatedly negative as were stool cultures for pathogenic bacteria. Several blood cultures showed no growth. Blood chemical determinations revealed alkaline phosphatase 3.5 B.U. per cent, urea nitrogen 16 mg. per cent, trace of bilirubin, albumin 4.6 Gm. per cent, globulin 2.8 Gm. per cent and euglobulin 0.6 Gm. per cent. There was 70 per cent retention of BSP in thirty minutes. The cephalin-cholesterol flocculation and the thymol turbidity tests were negative. Various x-ray and fluoroscopic examinations showed normal heart and lungs, marked splinting of the right diaphragm, a duodenal ulcer, a tender irritable and deformed cecum and a constant area of spasm in the hepatic flexure. A cholecystogram and intra-

venous pyelogram were normal. The amebiasis complement fixation test was ++.

After admission the patient received 4,000,000 units of penicillin daily for 17 days without effect upon fever or pain. The temperature which had been 102°F. on admission fell to 100°F. and remained there for a week at which time it spiked over a three-day period to 103.6°F. Chloroquine was then administered in doses of 0.6 Gm. of the base for two days followed by 0.3 Gm. of the base for nineteen days. By the third day of this treatment there was no fever and the liver which had been extremely tender and enlarged to two finger-breadths below the costal margin gradually decreased in tenderness and size and after a week was normal to percussion and palpation. The white blood count dropped from 15,900 to 7,200; the ESR from 31 to 2 mm.; the BSP from 20 per cent retention to none.

About one week after discontinuation of chloroquine the patient developed a crampy pain which began in the right upper quadrant and passed to the left upper quadrant which was relieved by defecation. This was accompanied by a rise in temperature to 100° to 101°F. Despite the pain and fever there was neither enlargement nor tenderness of the liver. Because of the presence of a duodenal ulcer an ulcer diet was prescribed but gave no relief. In view of this and because the white blood count, sedimentation rate and liver function tests remained normal and since the barium enema again revealed inflammatory changes in the cecum and hepatic flexure, it was decided that this episode might be due to amebic colitis. Accordingly, the patient was placed on diodoquin in doses of 1.89 Gm. daily for three weeks and an additional course of chloroquine. Under this regimen there was prompt and permanent alleviation of the fever and crampy pains. The patient gained 15 pounds in weight in the succeeding ten months during which he has been asymptomatic and his liver normal to physical and chemical examination. The amebiasis complement fixation test which initially was ++ is now ±.

CASE VI. M. H., No. 59087. A twenty year old American-born white housewife who had not traveled outside the general metropolitan New York area was admitted to the Methodist Hospital, Brooklyn, in May, 1948, and again in June, 1948, for treatment of amebiasis.

Previous history included an appendectomy

at the age of sixteen. The present illness began following a normal delivery in December, 1947. It consisted of fatigue, anorexia, 11 pound weight loss, fever, headaches and abdominal cramps associated with up to fifteen watery, mucoid and occasionally bloody stools a day.

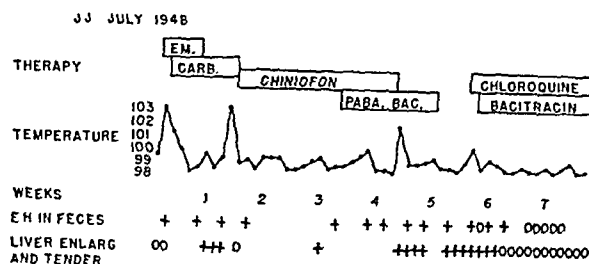


FIG. 3. Chart in Case VI.

The episodes of diarrhea lasted from three days to two weeks and occurred four times between December, 1947, and May, 1948. At this time physical examination revealed generalized abdominal tenderness and proctoscopy showed a bleeding granular mucosa. Stool examination revealed trophozoites and cysts of *Endameba histolytica*. The blood count was not remarkable except for a 14 per cent eosinophilia. X-ray of the chest was negative. During the first admission the patient received emetine subcutaneously, 60 mg. daily for eight days, and was started upon diodoquin 1.89 Gm. daily for seventeen days. After emetine therapy was completed she was discharged from the hospital to continue the diodoquin at home. While still on this drug, she again developed nausea, cramps and bloody diarrhea because of which she was readmitted. At this time a very tender mass in the right lower quadrant had developed. Amebas were still present in the feces and the complement fixation test for amebiasis was positive. The white blood count ranged from 6,000 to 15,000 with a persistent eosinophilia of from 11 to 30 per cent. The cephalin-cholesterol flocculation test was negative on the first occasion, positive later and finally negative. The thymol turbidity test was negative. The serum albumin was 3.1 Gm. per cent and the globulin 3.0 Gm. per cent. The serum alkaline phosphatase was 3.4 B.U. per cent. Serum agglutination tests were negative for typhoid O and H, paratyphoid A and B, *Brucella abortus* and *Proteus* X19. Urinalyses were normal in respect to specific gravity, protein, reducing substances and microscopic examination with the exception of microscopic hematuria on two occasions while sulfonamides were being administered. Stool

cultures failed to grow out pathogenic enteric bacteria.

Because of chills, fever, the tender abdominal mass and stools containing gross blood and pus, the patient (Fig. 3) was given during the first week 2.5 million units of penicillin, 10.5 Gm. of streptomycin, and 38 Gm. of sulfadiazine, along with 300 mg. of emetine and 6.5 Gm. carbarsone. Despite this on the seventh day the patient developed right upper quadrant pain associated with a tender liver which extended three finger-breadths below the costal margin while amebas persisted in the feces. On the tenth hospital day following the intravenous administration of parenamine, a pyrogenic reaction occurred followed by a thrombophlebitis in the left arm at the injection site. The next antiamebic drug to be used was chiniofon in daily doses of 0.75 Gm. for nineteen days, during the last seven days of which paraaminobenzoic acid¹⁰ was also administered in doses of 5.5 Gm. daily. Then bacitracin, which is currently under investigation as an intestinal amebicide,^{11,12} was administered by mouth in doses of 40,000 units daily for five days. Despite these drugs the liver remained enlarged and tender, the right lower quadrant mass was still present, bloody diarrhea persisted and *Endameba histolytica* was still found in the feces. At this time chloroquine in daily doses of 0.3 Gm. of the base was given for fourteen days. On the second day of chloroquine treatment the liver was less enlarged and much less tender, and after the fourth day of therapy it was neither palpable nor tender. Following the improvement in the hepatitis under chloroquine, oral bacitracin was re-administered in larger doses, 80,000 units daily for thirteen days. Under the combined therapy the stools became negative for *Endameba histolytica* and the right lower quadrant mass gradually disappeared. The patient regained and maintained good health during the succeeding five months during which repeated stool examinations have been negative.

In connection with the eosinophilia, there was no history of allergies or trichinosis nor were ova or larvae of helminths demonstrated in the stools. Five months later the white blood count was 6,450 with only 4 per cent eosinophilia.

CASE VII. P. H., No. 922146. A forty-six-year old white native of Argentina was admitted to the Presbyterian Hospital in September, 1948, complaining of chills, fever and sweats of three days' duration. He had "colitis" of

many years' duration, manifested by episodes of diarrhea which was occasionally bloody. Three months prior to admission *Endameba histolytica* had been demonstrated in his feces following which he received injections of emetine and strychnine. No oral amebicidal treat-

A.C. SEPT. 1948

DAYS 1 2 3 4 5 6 7 8 9 10 11 12

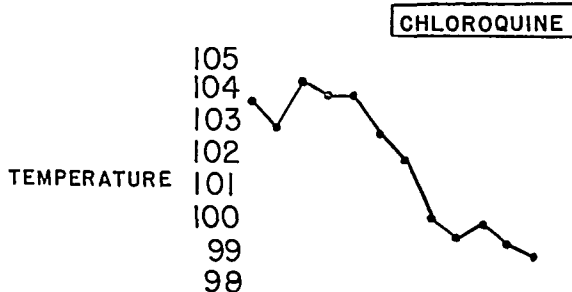


FIG. 4. Temperature chart in Case VII.

ment was administered. The present illness began on an airplane en route to New York. At the time of admission, physical examination revealed an acutely ill, febrile male exhibiting marked diaphoresis but with no localizing signs. On the third hospital day epigastric pain occurred along with an enlarged and tender left lobe of the liver. Laboratory tests revealed a leukocytosis of 17,000 with 86 per cent neutrophils, normal urinalysis, ESR of 74 mm., no malaria parasites, negative blood and stool cultures, negative Kline test, negative agglutination tests against typhoid, paratyphoid, *Brucella abortus* and *Proteus X19* organisms. The cephalin-cholesterol flocculation and thymol turbidity tests were negative. Serum alkaline phosphatase was 2.8 B.U. per cent and the serum bilirubin less than 0.5 mg. per cent. X-ray of the chest was negative except for evidence of strip atelectasis at the left base. Stool examination revealed cysts of *Endameba histolytica*. The amebiasis complement fixation test was anticomplementary initially and later positive.

Following admission (Fig. 4) fever and sweats persisted, and the left lobe of the liver became enlarged, tender and painful. Penicillin was administered beginning the second hospital day in doses of one half to one million units a day without effect. On the sixth hospital day chloroquine was administered in doses of 0.6 Gm. of the base for two days followed by 0.3 Gm. of the base daily. One and one-half days after the drug was started the temperature became normal



FIG. 5. Draining amebic abscess of the liver, Case VIII.

and the enlargement and tenderness of the liver gradually disappeared. After one week of chloroquine therapy the patient was discharged from the hospital, remained asymptomatic for one more week at which time he left the country.

CASE VIII. The patient was admitted to the Hospital for Tropical Diseases in London* with a discharging amebic abscess of the liver (Fig. 5) which had been opened surgically more than four months before and which had failed to heal despite intensive treatment, including several courses of emetine, as well as penicillin and streptomycin for various secondary infections that had supervened. Both the stools and the liver pus consistently revealed numerous trophozoites of *Endameba histolytica*. Because of the history of resistance to treatment the effects of various therapeutic agents were observed. Emetine was administered by various routes for nineteen days. (Fig. 6.) Emetine hydrochloride was injected subcutaneously for ten days in doses of 60 mg. daily for the first five days and then 90 mg. daily for the second five days. Emetine bismuthous iodide, 120 mg. a day, was given orally during the second five days. From the tenth to the nineteenth day a 0.012 per cent solution of emetine hydrochloride in physiologic saline was administered by continuous irrigation of the abscess cavity. In addition 1 million units of penicillin were given intramuscularly a day for the first five days.

* The data of this case were graciously supplied by Dr. F. Murgatroyd and Dr. N. H. Fairley of London.

Also given during the second five days were irrigations of the abscess cavity twice daily with 40 ml. of 0.1 per cent proflavine.

Under this regimen parasites disappeared from the feces but to support this aspect of the therapy diodoquin was administered orally in

an inflamed liver and, conversely, their absence from the feces does not necessarily imply their absence from an inflamed liver. Hence, in all but one case reliance has been placed upon the prompt disappearance of symptoms, signs and abnormal laboratory

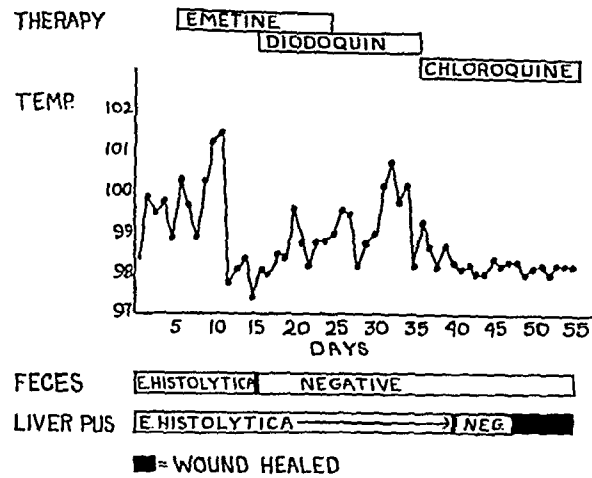


FIG. 6. Chart in Case VIII.

doses of 2.4 Gm. daily for twenty-one days. Despite all this amebas persisted in the pus discharging from the liver abscess. At this point administration of chloroquine was started in doses of 0.75 Gm. daily for eighteen days. Fever promptly disappeared. From the fifth day of chloroquine treatment amebas could no longer be found in the liver pus. By the twelfth day the discharge had ceased and the wound was healed. Two weeks following treatment the patient was discharged from the hospital and was prescribed a maintenance dose of 0.25 Gm. of chloroquine biweekly for three months. Two months after discharge from the hospital the patient continued to be in good health, was asymptomatic, had gained seventeen pounds, the wound was soundly healed, there was neither tenderness nor obvious enlargement of the liver, no amebas were found in the stool and the blood count was normal.

COMMENTS

It is recognized that there are perils in establishing a diagnosis without isolation of the etiologic agent from the organ involved. Because it did not seem justified, liver biopsy in the suspected presence of *Endameba histolytica* was not performed. The presence of amebas in the feces does not necessarily imply their presence within

TABLE III
SUMMARY OF PERTINENT SIGNS AND LABORATORY TESTS

	Present or Positive	Absent or Negative
Chills.....	7	1
Fever over 102°F.....	7	1
Hepatic enlargement.....	8	0
Hepatic tenderness.....	8	0
Diaphragmatic pleurisy.....	4	3
Icterus.....	0	8
E. histolytica in feces.....	7	1
E. histolytica in liver pus.....	1	
Amebiasis complement fixation test.....	5	
Cephalin-flocculation test.....	1	6
Bromsulfalein retention.....	4	
Elevated alkaline phosphatase.....	2	4

tests indicative of hepatitis following drug administration. Table III summarizes the objective evidence that these patients had hepatitis as well as amebiasis. The fact that the hepatitis in each instance began to clear within one to two days and progressively improved without recurrence is the critical element in establishing the activity of chloroquine against hepatic amebiasis. Needless to say, none of the patients had active malaria. Chloroquine has been administered without apparent benefit or detriment in the presence of acute infectious hepatitis.¹³ The only other hepatic disease known to be affected by chloroquine is infection with *Clonorchis sinensis*¹³ which was not present in any of the patients reported. Furthermore, in these patients no agent which is known to infect the liver other than *Endameba histolytica* was demonstrated. It consequently appears that the salutary effects observed in these patients may properly be ascribed to the effect of chloroquine upon infection of the liver with *Endameba histolytica*.

For the treatment of extra-intestinal amebiasis, the commonest lesion of which is found in the liver as diffuse inflammation with or without abscess formation, emetine is highly effective and may serve as a standard of reference for compounds with similar activity. So far as the patients who received chloroquine alone are concerned, the response to medication seemed just as prompt and as complete as would have been expected had emetine been used. Cases I, VI and VIII afford a comparison between chloroquine and emetine. It will be noted that even in this small series emetine is not uniformly effective in the treatment of amebic hepatitis or amebic abscess of the liver. The fact that chloroquine administered subsequent to the inadequate response to emetine was in each instance successful is significant, but is not to be taken as a prediction that the antiamebic activity of chloroquine will subsequently prove always to be superior to that of emetine.

It may well be possible to revise downward the daily dose and/or the duration of treatment with chloroquine for amebic hepatitis. With so few cases for study this was not attempted other than to vary the duration from two to four weeks and to omit the priming dose in two instances. On the other hand, upward revision of the daily dose and/or duration of treatment, if tolerated, might yield superior results in amebic colitis.

Toxicity of Chloroquine. Chloroquine causes only minor toxic manifestations. With antimalarial doses (1.2 to 1.5 Gm. of the base over one to three days) the following symptoms are infrequently observed: mild and transient headache, disturbance of visual accommodation, pruritus and gastrointestinal complaints.^{1,2,14} Chronic toxicity studies^{2,15,16} in humans have not disclosed any serious toxic symptoms or signs. Chloroquine in the dosage schedule employed in the treatment of amebiasis, namely, 0.6 Gm. of the base daily for two days, followed by 0.3 Gm. of the base daily for an additional twelve or nineteen days, has been administered to

forty patients, three of whom complained of nausea, one of transient pruritus and one of disturbed ocular accommodation. In no instance was the complaint of any magnitude and it was never necessary to interrupt or discontinue medication. Another patient reported by Most¹⁷ received concurrently chloroquine, emetine and diodoquin and developed generalized pruritus followed by mild epithelial desquamation, both of which began and terminated within one week. It might be significant that because of the combination of chloroquine and diodoquin, considerably more quinoline was being administered than if either had been used alone.

It is not the purpose of this paper to discuss the toxicity of emetine other than to mention that it does occur in the form of nausea, vomiting and diarrhea, and occasionally in the form of severe myositis and myocarditis. Chloroquine presents no such serious toxic potentialities and in addition does not require parenteral administration.

Correlation of Drug Localization with Activity. A disparity between the results obtained with various antiamebic agents, depending upon the location of the infection, has long been known to exist. Emetine has typified one fashion of activity in that it is highly effective in extra-intestinal amebiasis whereas when used alone it succeeds in eliminating permanently the ameba in only 10 to 15 per cent of cases of colitis.¹⁸ The iodohydroxyquinolines, on the other hand, are said to be effective in 70 to 90 per cent of intestinal infections but are without effect in extra-intestinal infections.

One explanation offered for this dichotomy of action has assumed a differential *in vivo* activity of these compounds against trophozoites and cysts. This concept, however, is based upon a fundamental misunderstanding of the pathogenesis of amebiasis. Amebic infection (Fig. 7) is established in the colon following the ingestion of cysts by their excystment into trophozoites which then invade the colonic mucosa. Following this either cysts or trophozoites may appear in the feces. Thus the form of

Endameba histolytica which is responsible for the initiation and perpetuation of colonic or metastatic infection is the trophozoite, and it is this which must be eradicated in order to cure the infection. Were the differential elimination of cysts in the colon

PATHOGENESIS OF HUMAN AMEBIASIS

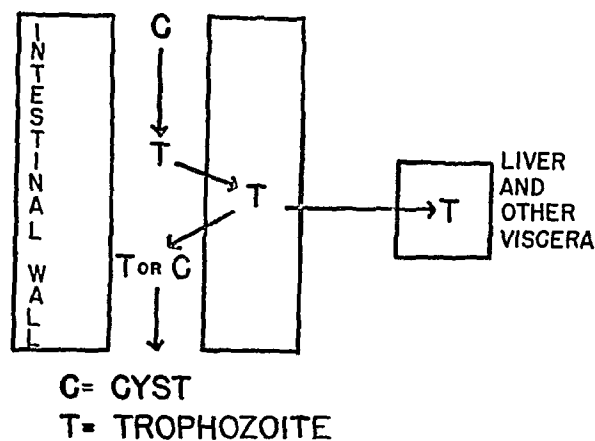


FIG. 7. A schematic drawing of amebic infection.

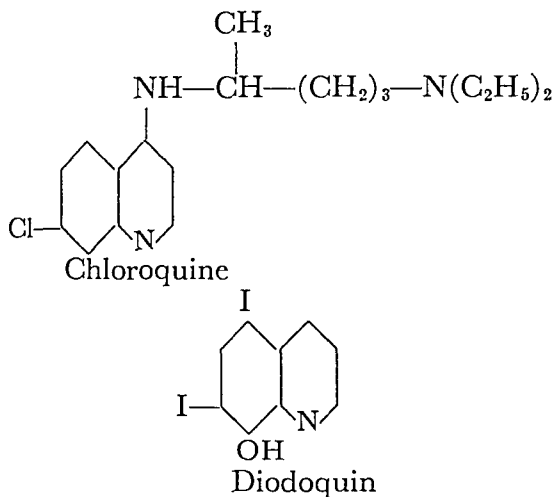
possible the trophozoites and hence persistent infection would remain. Hence the significance of the cyst in the feces is that its presence is not of importance to the disease of the host in whom it is only diagnostic of trophozoites activity within the colon, but is of importance as a means of infecting another host.

A more rational hypothesis may be constructed upon the degree of drug localization within infected tissues. One of the basic premises of this study was that if chloroquine had any *in vivo* antiamebic activity, it would be most apparent against amebas in the liver because of the high drug localization in that organ, and less apparent against amebas in the intestine because of the lesser degree of localization there. That the clinical results follow this pattern does not establish the point but it is of correlative interest that the recently published information of Parmer¹⁹ and Smith et al.²⁰ concerning the tissue distribution of emetine indicate that it parallels that of chloroquine in regard to the intestinal wall, liver and

other organs. Also in accord with this hypothesis is the efficacy of the iodohydroxyquinolines in intestinal amebiasis as opposed to their ineffectiveness against extraintestinal amebiasis. This can be correlated with the very small degree of absorption and consequently high intestinal concentration of these compounds which has been reported by Albright, Tabern and Gordon²¹ in regard to chiniofon.

Chance et al.²² have noted that in proportional doses a greater hepatic and intestinal localization of arsenic with trivalent arsine oxides occurs than with pentavalent arsonic acids to which class belong carbarsone, acetarsone, treparsol, etc. Such information may explain why carbarsone, a rather efficient intestinal amebicide, has proven ineffective in extra-intestinal amebiasis. Anderson et al.²³ have found that certain arsine oxides, such as carbarsone oxide (the trivalent analog of carbarsone) and its dithiocarboxymethyl and dithiocarboxyphenyl derivatives possess amebicidal activity *in vitro* and in macaques greater than that of carbarsone. In animals the thioarsenites, as anticipated, were less toxic than their parent compound. Subsequently Anderson et al.²⁴ have successfully treated three patients with amebic hepatitis with thioarsenites. This is of considerable pharmacologic interest because it indicates that, like 4-aminoquinolines, arsenic can be delivered to the liver in therapeutic concentrations.

Presumably because of the lethal effect of iodine upon cysts of *Endameba histolytica in vitro*, the activity of the iodohydroxyquinolines upon trophozoites in human infections has been attributed to their iodine content. One compound is recommended because it contains twice as much iodine as others yet paradoxically is given in nearly twice the dosage of similar compounds with less iodine. A comparison of the formula of chloroquine, which contains no iodine, with that of diodoquin as a representative of the iodohydroxyquinolines reveals the quinoline nucleus as a common denominator.



This suggests that the quinoline nucleus or some metabolic degradation product thereof, rather than the iodine content, may represent the active amebicidal component in these compounds.

If the effects of amebicidal drugs are truly correlated with their localization in sufficient concentrations within selected tissues, the idea may be entertained that a single quinoline derivative may be found which can be administered in non-toxic dosage with the achievement of adequate amebicidal concentration within the intestine as well as the liver and other viscera which may be involved in amebiasis.

Role of Chloroquine in the Treatment of Amebiasis. Because it is clinically impossible to determine with accuracy in every case of intestinal amebiasis whether or not extra-intestinal involvement has occurred, and because of the high frequency of such metastatic infection observed in pathologic material,¹⁸ it is at least theoretically highly desirable to treat every patient with intestinal amebiasis with agents designed to eradicate amebae wherever they may be in the body. Until now emetine has been the only available agent for extra-intestinal amebiasis whereas there are several fairly efficient intestinal amebicides. The toxicity of emetine and the measures designed to minimize or prevent such toxicity have precluded the widespread practical application of the above principle. Since the lack of toxicity of chloroquine permits treatment

of even ambulatory patients, it is recommended that chloroquine be employed in addition to a more efficient intestinal amebicide for the treatment of all cases of intestinal amebiasis. Conversely, for the treatment of hepatic amebiasis, even in the absence of signs or symptoms of intestinal involvement, it is recommended that an intestinal amebicide be employed in addition to chloroquine in order to be more certain to eradicate any colonic focus of infection, because chloroquine is only about 50 per cent curative for intestinal amebiasis. Case v illustrates this point.

Because of the widespread use of chloroquine in the suppression of malaria, it would be profitable to determine whether this compound possesses any antiamebic suppressive or prophylactic properties.

CONCLUSION

Chloroquine is a safe and effective chemotherapeutic agent for the treatment of amebic infections of the liver, being at least as effective as emetine but without the toxicity of emetine. The combination of chloroquine with a superior intestinal antiamebic drug should permit adequate treatment of any amebic infection, and should permit wider use of antiamebic chemotherapy as a diagnostic and therapeutic test in obscure infections of the liver and intestine.

ACKNOWLEDGMENT

For the privilege of studying and treating their patients, the author is deeply indebted to the following: Drs. F. K. Heath, A. R. Lamb, Sr., and G. C. Hennig of the Presbyterian Hospital, Dr. C. M. Guest of the Veterans Administration Hospital, Bronx, and Dr. J. A. Head of the Methodist Hospital, Brooklyn.

Acknowledgment has already been made to Drs. F. Murgatroyd and N. H. Fairley of London for supplying the data in Case VIII.

The author wishes to thank Mrs. C. R. Demarest without whose competent parasitologic studies this work would have been impossible.

The author is grateful to Dr. H. W. Brown

for performing the *in vitro* drug tests and the complement fixation tests.

Finally, the author wishes to express his appreciation to Dr. R. F. Loeb for his invaluable aid and encouragement in the conception and performance of this study.

REFERENCES

1. LOEB, R. F., CLARK, W. M., COATNEY, G. R., COGGESHALL, L. T., DIEUADE, F. R., DOCHEZ, A. R., HAKANSSON, E. G., MARSHALL, E. K., JR., MARVEL, C. S., MCCOY, O. R., SAPERO, J. J., SEBRELL, W. H., SHANNON, J. A. and CARDEN, G. A., JR. Activity of a new antimalarial agent, chloroquine (SN-7618). Statement approved by the Board for Coordination of Malarial Studies. *J. A. M. A.*, 30: 1069, 1946.
2. BERLINER, R. W., EARLE, D. P., JR., TAGGERT, J. V., ZUBROD, C. G., WELCH, W. J., CONAN, N. J., JR., BAUMAN, E., SCUDDER, S. T. and SHANNON, J. A. Studies on the chemotherapy of the human malaras. vi. The physiological disposition, antimalarial activity, and toxicity of several derivatives of 4-aminoquinoline. *J. Clin. Investigation*, 27: 98, 1948.
3. SCHMIDT, L. H. Personal communication.
4. DENNIS, E. W. Personal communication.
5. CONAN, N. J., JR. Chloroquine in amebiasis. *Am. J. Trop. Med.*, 28: 107, 1948.
6. SHOOKHOFF, H. B. Personal communication.
7. SODEMAN, W. A. Personal communication.
8. MURGATROYD, F. Personal communication.
9. MURGATROYD, F. and KENT, R. P. Refractory amoebic liver abscess treated by chloroquine. *T. Roy. Soc. Trop. Med. & Hyg.*, 42: 15, 1948.
10. DWORK, K. G. The use of para-aminobenzoic acid in amebiasis; preliminary report. *Bull. New York Acad. Med.*, 24: 391, 1948.
11. LONGACRE, A. Personal communication.
12. MOST, H., GROSSMAN, E. B. and CONAN, N. J., JR. Unpublished data.
13. CONAN, N. J., JR. Unpublished data.
14. MOST, H., LONDON, I. M., KANE, C. A., LAVIETES, P. H., SCHROEDER, E. F. and HAYMAN, J. M., JR. Chloroquine for the treatment of acute attacks of vivax malaria. *J. A. M. A.*, 131: 963, 1946.
15. ALVING, A. S., EICHELBERGER, L., CRAIGE, B., JR., JONES, R., JR., WHORTON, C. M. and PULLMAN, T. N. Studies on the chronic toxicity of chloroquine (SN-7618). *J. Clin. Investigation*, 27: 60, 1948.
16. CRAIGE, B., JR., WHORTON, C. M., JONES, R., JR., PULLMAN, T. N., ALVING, A. S., EICHELBERGER, L. and ROTHMAN, S. A lichen-planus-like eruption occurring during the course of chloroquine administration. *J. Clin. Investigation*, 27: 56, 1948.
17. MOST, H. Personal communication.
18. CRAIG, C. F. The Etiology, Diagnosis, and Treatment of Amebiasis. Baltimore, 1944. William & Wilkins Company.
19. PARMER, L. G. On the relative efficacy of emetine in intestinal and hepatic amebiasis. *Proc. Soc. Exper. Biol. & Med.*, 68: 362, 1948.
20. SMITH, P. K., GIMBER, A. I. and DAVISON, C. The tissue distribution and toxicity of emetine. *Federation Proc.*, 7: 256, 1948.
21. ALBRIGHT, E. C., TABERN, D. L. and GORDON, E. S. The metabolism of chiniofon using radioactive iodine. *Am. J. Trop. Med.*, 27: 553, 1947.
22. CHANGE, A. C., CRAWFORD, T. B. B. and LEVY, G. A. The fate of arsenic in the body following treatment of rabbits with certain organic arsenicals. *Quart. J. Exper. Physiol.*, 33: 137, 1945.
23. ANDERSON, H. H., HANSEN, E. L., SAH, P. P. T. and CAFISO, J. R. Amebicidal and pharmacologic activities of carbarsone oxide (p-carbamidophenyl-arsenous oxide) and its dithiocarboxymethyl and dithiocarboxyphenyl derivatives. *J. Pharmacol. Therap. & Exper.*, 91: 112, 1947.
24. ANDERSON, H. H., JOHNSTONE, H. G. et al. Thioarsenites in amebiasis. *J. A. M. A.* (In press.)

Liver Function during Infectious Mononucleosis*

JOHN W. BROWN, M.D., JOHN LEROY SIMS, M.D., EDWARD WHITE, M.D.
Madison, Wisconsin *Alameda, California*
and JACK E. CLIFFORD, M.D.
Boise, Idaho

DURING the course of infectious mononucleosis manifestations of involvement of various organs have been observed.¹⁻¹¹ The few postmortem examinations which have been made revealed the presence of widespread abnormalities.^{12,13,14} Evidence of hepatitis was demonstrated in each of these studies, and by biopsy in others.¹⁵⁻¹⁸ Jaundice was observed during infectious mononucleosis over twenty years ago and subsequently in occasional cases.^{19,20,21} Investigation of its pathogenesis has been made only recently.

Several series of cases of infectious mononucleosis have now been reported in which tests of liver function revealed abnormalities in a significant proportion.^{9,22-25} The results are, in general, similar to those obtained during infectious hepatitis.²⁶ Many cases of infectious mononucleosis resemble those with infectious hepatitis of virus etiology and the differentiation by either clinical or laboratory means is often difficult.^{26,27}

Since the etiology of the condition is not established, accurate specific criteria for its diagnosis are not available. It has been shown that the clinical features are so variable that the absence of the typical syndrome does not exclude the disease.^{2,3,9,10} It is fair to state that the diagnosis of infectious mononucleosis in the individual case at present must be presumptive and based upon clinical manifestations supported by information supplied by nonspecific laboratory tests. Several virus infections provide features commonly associated with

infectious mononucleosis. German measles and, as indicated, infectious hepatitis are among the most difficult to differentiate. The evidence suggests that infectious mononucleosis is a specific infectious disease entity, but the possibility exists that the various manifestations are part of a syndrome which may be caused by one of several etiologic agents. Accurate evaluation of the significance of changes in liver function during infectious mononucleosis will require extended observation of patients after recovery and further correlation by clinical, biopsy and postmortem examinations.

It is the purpose of this report to present the results obtained by observation and liver function tests made during the study of a series of eighty-three cases in which the diagnosis of infectious mononucleosis was made.

METHODS

Liver function tests were performed during the course of infectious mononucleosis in eighty-three cases which were observed in the Department of Student Health of the University of Wisconsin from August, 1946, to June, 1948. All patients were between seventeen and thirty-four years of age. Fifty-five were men. All but two were hospitalized for varying periods. For the purpose of this study the diagnosis of infectious mononucleosis was made if the clinical features were clearly suggestive and either an increased lymphocyte percentage of the white blood cell differential count, with the appearance of abnormal forms, was present in the peripheral blood or a rise in heterophile anti-

* From the Departments of Medicine and Preventive Medicine and Student Health, University of Wisconsin Medical School, Madison, Wis. Supported in part by the Research Grants Division of the U.S. Public Health Service.

bodies to a titer of 1:128 or above occurred in the serum. Heterophile antibodies were not demonstrated in the serum of fifteen of the patients included. In eight of these the test was made only once, in each instance before the tenth or after the twentieth day. Four additional patients had a maximum titer of 1:64. The presence of other characteristic features seemed to justify the inclusion of these nineteen cases. The limitations to specific diagnosis, expressed in the foregoing, are accepted as applying fully to the cases of this series. The series is consecutive in that it includes all cases in which infectious mononucleosis was considered established with reasonable certainty by the existing criteria and which had one or more tests of liver function performed at random or in series. Most patients had two or more tests performed several times. During this period many other patients were encountered, some as outpatients, who probably suffered from this condition but they are omitted because of the absence of confirmatory laboratory data.

The heterophile antibody determinations were made by the method of Davidsohn.^{28,29} The absorption technic was employed. Liver function tests included icterus index, seventy-four cases; qualitative urine urobilinogen excretion, sixty-eight cases; cephalin cholesterol flocculation test, eighty-two cases; thymol turbidity test, seventy-seven cases; prothrombin time, thirty-nine cases and bromsulfalein dye retention, sixty-two cases. Urobilinogen excretion was considered abnormal if the urine dilution of 1:80 or more was positive by the Wallace-Diamond test.³⁰ For the cephalin cholesterol flocculation test values of +++ or more in twenty-four hours were interpreted as abnormal, and for the thymol turbidity test 4 units or more. The methods of Hanger and MacLagan, respectively, were used.^{31,32} Results of ++ and 2 units or more, respectively, for these tests are also recorded since these lower figures may be of significance.³³ The lowest normal value for prothrombin time was considered to be 75 per cent. The technic of Quick was used and the value expressed in per cent of normal.³⁴ For the early cases the bromsulfalein test was performed by the intravenous injection of 2 mg. of dye per Kg. of body weight, the amount retained in the blood being measured in twenty minutes. Significant retention rarely occurred. For the last forty-one cases an injection of 5 mg. of dye per Kg. of body weight was used and the per cent retained measured after thirty minutes.

With this method significant retention of dye was demonstrated frequently; a result of 10 per cent or more is listed as abnormal.

RESULTS

One or more liver function tests were abnormal in seventy-five of the eighty-three

TABLE I
SUMMARY OF THE RESULTS OF LIVER FUNCTION TESTS
DURING INFECTIOUS MONONUCLEOSIS IN EIGHTY-THREE PATIENTS

Tests Made One or More Times	Total Cases	Results		
		Values (Maximum obtained in each case)	No. of Cases	Per Cent
Icterus index.....	74	10 units or more	28	38
		20 units or more	7	
Urobilinogen excretion....	68	1:80 or more	23	34
Cephalin cholesterol flocculation.....	82	+++ or more	70	85
		++ or more	76	92
* Initial test.....		+++ or more	60	73
		++ or more	71	87
Thymol turbidity.....	77	4 units or more	38	49
		2 units or more	58	75
† Initial test.....		4 units or more	27	35
† Initial test.....		2 units or more	47	61
Prothrombin time.....	39	Below 75% (Minimum 57%)	5	13
Bromsulfalein.....	62			
2 mg., 20 min. technic..	21	10% retention	1	
		5% retention	2	
		0% retention	18	
5 mg., 30 min. technic..	41	10% retention or more	20	49
		50% retention	2	
		40% retention	1	
		35% retention	5	
		30% retention	2	
		25% retention	1	
		20% retention	2	
		15% retention	3	
		10% retention	4	
		Less than 10% retention	21	

* The initial test (in some cases the only test) was made between the third and sixty-second day of disease, all but four before the eighteenth day.

† The initial test (in some cases the only test) was made between the third and seventy-ninth day of disease, all but six before the eighteenth day.

cases in this series. A general summary of the results and the comparative frequency of abnormal figures obtained with the various tests employed are presented in Table I. The data obtained in several representative individual cases is contained in Table II. Table III summarizes the findings in patients who had serial cephalin cholesterol flocculation and thymol turbidity tests made.

The cephalin cholesterol flocculation test was abnormal in 85 per cent of the eighty-

TABLE II

SUMMARY OF STUDIES IN FIFTEEN INDIVIDUAL PATIENTS WHO HAD SERIAL LIVER FUNCTION TESTS DURING
INFECTIOUS MONONUCLEOSIS

Patient Sex, Age, Onset	Date of Test	Blood		Hetero- phile Antibody Titer	Icterus Index (units)	Urine Urobil- inogen (Dilu- tion Positive)	Cephalin C o- lesterol Floccu- lation	Thymol Tur- bidity (units)	Brom- sulfalein Reten- tion Per Cent	Pro- throm- bin Per Cent	Clinical			
		Total W.B.C. × 1000	Lympho- cytes Per Cent								Days in Hos- pital	Severity	Spleen Palpa- ble	Days of Fever 100°F. or over
M. K. F, 18	1/20/47	9 2	50	0	.	0	25	Mod.	0	10
1/11/47	1/23	10 6	70	.	.	.	++	.	.	.				
	1/27	16 35	75	256	9	.	++++	3	.	.				
	2/5	8.9	56	.	.	.	+++	.	.	.				
	4/4	9 0	26	.	7	.	0	0	.	100				
L. Y. M, 27	1/25/47	13.3	66	512	11	17	Mod.	+	9
1/14/47	1/27	.	.	.	9	.	++++	.	.	80				
	1/29	.	.	.	5	.	++++	5	.	80				
	3/27	8.5	31	128	5	1:160	+++	5	0*	85				
	4/22	1:40	+	1	.	.				
P. S. F, 20	2/11/47	8 4	76	256	17	Mild	+	14
2/5/47	2/21	10 95	68	.	5	.	++++	.	.	100				
	3/19	9.55	27	512	5	.	+++	5	0*	100				
	4/8	10 75	35	128	4	1:80	+++	3	.	100				
	4/29	.	.	64	.	1:10	++	.	.	.				
R. S. M, 19	2/20/47	8 6	36	.	10	0	++	0	0	.	20	Severe	+	9
2/14/47	2/24	9 3	83	1024	.	1:160	++++	4	.	66				
	3/3	12 1	71	.	.	1:320	+++	6	0*	100				
	3/19	7.4	67	512	.	.	+++	5	5	.				
	4/8	9 0	62	512	6	1:40	++++	5	0	90				
	4/22	8 3	35	256	8	1:80	++++	1	.	85				
W. J. M, 20	2/18/47	18 0	81	256	.	1:40	+	.	.	.	16	Mod.	0	4
2/16/47	2/21	.	.	.	5	.	+++	1	.	100				
	2/24	13 0	71	128	.	.	+++	2	.	.				
	3/19	8 6	44	64	10	1:20	+++	3	0*	100				
	4/8	7 0	53	32	7	1:40	+	1	.	100				
M. W. F, 20	2/26/47	9.65	76	1024	9	Mild	0	7
2/20/47	3/1	16 15	67	.	9	.	+++	0	.	100				
	3/19	2 45	19	1024	4	1:40	+++	1	0*	100				
	4/8	9 0	30	512	4	0	0	1	.	85				
G. D F, 21	2/26/47	11 5	82	2048	7	Mild	0	0
2/22/47	3/3	10 2	63	1024	6	1:200	+++	1	.	100				
	3/19	6 65	51	1024	5	1:160	+++	5	0*	100				
	4/8	7 45	29	512	4	1:40	0	0	.	100				
	5/20	8 9	33	128	.	1:80	++	0	.	.				
M. E. F, 18	3/6/47	6 25	57	0	15	Mod.	+	8
2/25/47	3/19	10 1	83	256	5	1:20	++++	5	0*	100				
	3/27	10.0	74	128	4	.	+++	7	0	100				
	4/8	8 5	37	32	6	1:40	+++	5	.	100				
	4/29	1:40	+++	2	.	.				
B. H. F, 24	8/15/47	7	61	.	9	1:20	+	1	40†	.	3	Mild	0	2
8/10/47	9/8	6 9	44	64	10	1:20	+++	5	0	.				
D. S. M, 23	10/20	1:20	0	3	0	.				
8/11/47	8/18/47	20	68	256	10	1:60	+++	3	35†	.	20	Mod.	+	2
	9/4	7 5	28	.	10	1:20	+++	7	0	.				
	9/18	.	.	.	9	0	0	3	0	.				
	10/23	.	.	.	7	0	0	2	0	.				
C. E. M, 34	1/13/48	5 0	21	0	6	1:40	0	1	.	.	22	Mild	+	10
1/5/48	1/15	6 0	47	256	6	.	+++	.	.	.				
	1/19	.	.	.	9	.	+++	3	15†	.				
	2/2	.	.	.	6	.	+++	2	0	.				
	2/13	0	0	1	.	.				
G. L. F, 18	1/14/48	18 9	73	0	.	.	+++	.	.	.	19	Mod.	+	0
1/8/48	1/19	.	.	.	9	1:20	+++	5	0†	.				
	2/9	5 95	54	0	0	0	+++	3	.	.				
	3/30	7 0	22	.	5	.	++	1	.	.				
R. L. M, 19	2/7/48	11.0	78	0	30	1:320	.	5	.	.	18	Mod.	+	7
1/31/48	2/9	.	.	.	20	.	0	5	30†	.				
	2/10	.	.	.	20	.	+++	.	.	.				
	2/16	8 85	78	128	10				
E. E. M, 20	3/4/48	8 0	69	0	7	1:80	++	2	0†	.	16	Mild	+	8
2/29/48	3/9	12 0	50	128	.	.	+++	.	.	.				
	3/21	.	.	0	10	1:20	+++	5	0	.				
	4/9	7 0	52	.	5	1:20	0	3	.	.				
J. B. F, 19	3/19/48	20	52	512	25	1:80	+++	9	50†	.	19	Mod.	+	7
3/10/48	3/25	9	73	.	12	1:40	.	9	.	.				
	4/2	6	40	.	.	.	+++	.	.	.				
	4/5	9	57	.	.	1:20	+++	.	0	.				

* 2 mg., twenty-minute method
† 5 mg., five-minute method

two cases in which it was done one or more times and on at least one occasion in thirty-eight of thirty-nine cases who had the test three or more times. A result of +++ or more was obtained in sixty of the eighty-two cases at the time the first test was made (in

TABLE III
INCIDENCE OF POSITIVE CEPHALIN CHOLESTEROL FLOCCULATION AND THYMOL TURBIDITY TESTS WHEN DETERMINATIONS WERE MADE SERIALLY IN PATIENTS WITH INFECTIOUS MONONUCLEOSIS

No. of Tests	Cephalin Cholesterol Flocculation			Thymol Turbidity				
	No. of Cases	Re-sult* +++ or More	Per Cent	No. of Cases	Re-sult* 4 Units or More	Per Cent	Re-sult* 2 Units or More	Per Cent
3 or more	39	38	97	29	19	66	26	83
2 or more	60	57	95	53	29	55	43	81

* Pertains to the highest value obtained in the series of tests in each patient.

some cases a single determination). The earliest day of the disease on which a cephalin cholesterol flocculation test was made varied in individual patients from the third to the sixty-second; all except four cases were tested before the eighteenth day. For the thirty-eight patients who had a series of three or more tests the average time from the estimated onset of the disease to the day on which the last result of +++ or more was obtained was thirty days. (Table iv.) For eight of these the final value was +++ or more at ten, fifteen, fifteen, twenty-three, twenty-six, thirty-two, fifty-six and sixty-three days, respectively. The duration of abnormal flocculation beyond this in these patients is unknown. Flocculation of ++ or more occurred on the average for forty-four days. During convalescence the interval between examinations was two to three weeks for many cases so that abnormal flocculation undoubtedly persisted longer on the average than these figures indicate. The cephalin cholesterol flocculation test was positive in twelve of the fifteen cases in which heterophile antibodies were not demonstrated. In nine of the twelve the

two tests were made at the same time. The possibility that infectious hepatitis of specific virus etiology may have been present in those cases in which heterophile antibodies were not demonstrated is difficult to eliminate. During the period of this study pa-

TABLE IV
DURATION OF POSITIVE CEPHALIN CHOLESTEROL FLOCCULATION AND THYMOL TURBIDITY TESTS IN PATIENTS WITH INFECTIOUS MONONUCLEOSIS WHO HAD A SERIES OF THREE OR MORE TESTS

Test	Result	No. of Cases	Average Days*	Maximum Days*	Minimum Days*
Cephalin cholesterol..	+++ or more	38	30	79	6
flocculation.....	++ or more	38	44	290	9
Thymol turbidity....	4 units or more	19	35	74	12
	2 units or more	25	52	253	14

* Number of days from onset of disease to day on which the last test with the result indicated was obtained. In eight of these patients the cephalin cholesterol flocculation was +++ or more at the time of the last determination, ten, fifteen, fifteen, twenty-three, twenty-six, thirty-two, fifty-six and sixty-three days, respectively. In four the thymol turbidity value was 4 units or more when last examined, twenty-three, twenty-three, twenty-eight and fifty days, respectively.

tients with clearly recognizable infectious hepatitis were rarely encountered. The results obtained with the thymol turbidity test in seventy-seven patients are listed in the tables. It was positive in a significant proportion of cases but less frequently and, on the average, later in the course of the disease than the cephalin cholesterol flocculation test. The serum of four of the patients who had a series of tests showed values of 4 or more units when last examined at twenty-three, twenty-three, twenty-eight and fifty days, respectively. The thymol turbidity values were abnormal in seven of the fifteen cases in which heterophile antibodies were not demonstrated. Three of the seven had the tests made at the same time. The icterus index was 10 units or more in twenty-eight (thirty-eight per cent) of the seventy-four cases in which it was made. Seven of these had 20 units or more. The increase in icterus index, when it occurred, was present during the early acute phase in most instances. The highest result obtained for the thymol turbidity test was less than 4 units in nine cases and for the cephalin cholesterol flocculation test less than ++

in three cases of the total of twenty-eight in which the icterus index reached 10 units or more. Thymol turbidity was positive in the other nineteen cases and cephalin cholesterol flocculation in the other twenty-five cases who had an elevated icterus index. Abnormal amounts of urobilinogen appeared in the urine in twenty-three (thirty-four per cent) of the sixty-eight cases in which the test was made. The prothrombin time was below 75 per cent of normal in five of the thirty-nine patients tested. It did not reach significantly low levels in any patient.

The bromsulfalein test was abnormal in twenty (49 per cent) of the forty-one cases in which the 5 mg. per Kg. dose of dye was employed and the retention in the blood measured after thirty minutes. In all of these an increased retention of dye occurred during the first test; in all but one case (retention 10 per cent) the first test was made during the first two weeks of illness. Table v summarizes the results of three tests in forty-one cases who had bromsulfalein (5 mg., thirty-minute method), cephalin cholesterol flocculation and thymol turbidity tests. Cephalin cholesterol flocculation was positive when bromsulfalein retention was abnormal in all but one case. It was positive in eighteen cases in which bromsulfalein retention was not increased. The results of thymol turbidity tests did not correlate closely with bromsulfalein retention. (Table v.)

A comparison of the results of the liver function tests made in this series of cases of infectious mononucleosis indicates that the cephalin cholesterol flocculation was most frequently abnormal. It was positive early and for a significant length of time in nearly all cases.

A prolonged period of fatigability frequently occurs following infectious mononucleosis. However, the duration of subjective symptoms did not correlate with the results of liver function tests for the twenty-four patients of this series on whom sufficient information for evaluation during convalescence is available. Most of the patients

returned to school before all of the liver function tests had become normal. (Table II.) Treatment consisted of bed rest during the febrile period, activity as limited during convalescence as was possible when University work was resumed, and a high-

TABLE V
CORRELATION OF THE RESULTS OF THREE TESTS IN FORTY-ONE PATIENTS WITH INFECTIOUS MONONUCLEOSIS*
(The Most Abnormal Result Obtained for All Tests in Each Patient Is Used)

Result	Bromsulfalein Retention (5 mg., 30-min. technic)	Cephalin Cholesterol Flocculation		Thymol Turbidity	
		+++ or More No. of Cases	Less Than +++ No. of Cases	4 Units or More No. of Cases	Less Than 4 Units No. of Cases
10% or more.....	20	19	1	10	10
Less than 10%.....	21	18	3	11	10

* In all except five patients the tests were made on the same day.

protein, high-carbohydrate, low-fat diet for as long as practicable. Patients who had bacterial or fusospirochetal pharyngitis or tonsillitis during the course of the disease received penicillin by intramuscular injection. A relapse or clinical evidence of chronic liver disease was not observed.

COMMENTS

In this series of eighty-three cases of infectious mononucleosis tests of liver function revealed abnormal values in a significant proportion. From the results obtained it is reasonable to suggest that every patient with this condition will demonstrate abnormal liver function, as measured by the tests employed, during its course. The studies of other investigators have resulted in a similar conclusion.²²⁻²⁵ However, the clinical significance of the results of these liver function tests during infectious mononucleosis as a measure of hepatic involvement or damage is not certain. As far as we are aware, fatalities due to liver insufficiency during this disease have not been observed. Long term studies of liver function following infectious mononucleosis are not available and must await the passage of time. Investiga-

tions to date have revealed the tendency of liver functions to return to normal within two to six weeks. De Marsh and Alt report cases with abnormal values at three and four and one-half months, respectively.²³ Abrams⁴³ reports a case with visible jaundice for eleven weeks; Cohn and Lidman suggest that a patient under their observation was developing chronic hepatitis.²² In our series the cephalin cholesterol flocculation test was abnormal after eight and nine weeks, respectively, in two patients whose further course is unknown. Experience suggests that liver damage sufficient to cause insufficiency in later life is infrequently if ever incurred as the sequel to hepatitis during infectious mononucleosis.

In the present series the tests most frequently abnormal were the cephalin cholesterol flocculation and thymol turbidity. These are dependent upon alteration in the serum globulin components.³⁵⁻³⁷ The factors responsible for abnormal values for these tests as well as for retention of brom-sulfalein are suspected to reside in cells of the reticulo-endothelial system.³⁸ In the strict sense these tests are not direct measures of liver function. Nevertheless conditions other than hepatitis have been associated infrequently with similar abnormalities.^{25,33,36,44} The mechanism operating for serum alkaline phosphatase increase, employed as a test of liver function by Gall, is open to similar criticism.^{24,39,40} The evidence to date indicates that the mechanism of excretion of urobilinogen is dependent upon the parenchymal cells of the liver. Urinary excretion of urobilinogen was abnormal in a significant proportion of cases (34 per cent) in this series. Of necessity, the Wallace-Diamond dilution technic was used instead of the more reliable quantitative estimation of urobilinogen developed by Watson. White and co-workers found that while significant discrepancies between these two methods are unusual, individual variations are seen with sufficient frequency to lessen the value of the Wallace-Diamond technic as a single test.⁴¹ Since an elevation of icterus index in individual cases is not conclusive evidence of hepatocellular injury, the frequent ob-

servation of this circumstance does not provide proof of hepatitis. However, when the results of all of the tests performed in individual cases of infectious mononucleosis are evaluated, it is reasonable to conclude that actual hepatitis occurred in a significant proportion of the cases in this and other reported series. This conclusion is supported by the demonstration of hepatitis, as well as involvement of many other organs, in all of the postmortem studies which have been made.¹²⁻¹⁴

The problem of infectious mononucleosis is important because of its frequency and the evidence that many organs may be involved during the course.¹⁻¹¹ The reports that severe central nervous system involvement may be associated with this syndrome are of particular significance.^{4-10,14} The disease warrants intensive investigation from this standpoint. The spinal fluid was normal in the two cases of the present series in which it was examined.

Infectious mononucleosis is protean in its manifestations and diagnosis is often difficult. It may be responsible for many apparently minor illnesses. Since the etiology is unknown, the diagnosis at present must depend upon clinical judgment, blood examination and measurement of the heterophile antibody rise in the serum. Of these the only reasonably specific aid is the heterophile antibody test. The demonstration of an increase in heterophile antibodies is often difficult and exacting laboratory technics are required.^{28,29} A rise in heterophile antibodies is not usually present until after the first week of the disease. The titer falls rapidly in many cases and may be overlooked if serial tests are not made. Because of these considerations, several cases in the present series are included in spite of failure to demonstrate a rise of heterophile antibodies in the serum. Of diagnostic importance is the fact that a rise in heterophile antibody titer is not a recognized feature of infectious hepatitis of known virus etiology.²⁶

During infectious mononucleosis the cephalin cholesterol flocculation test becomes abnormal in the first few days of the disease in nearly all cases. It was positive in twelve

of the fifteen cases in which heterophile antibodies were not demonstrated. As suggested by Evans²⁵ this test often provides earlier and more uniform confirmatory evidence for the presence of infectious mononucleosis than the heterophile antibody determination if infectious hepatitis of viral etiology can be eliminated.

In our experience and that of others the differentiation between infectious mononucleosis and infectious hepatitis in occasional cases with or without jaundice has been difficult if not impossible by either clinical or laboratory means.^{9,10,25,26,27} As a result it is likely that mistakes in the diagnosis of these conditions are of frequent occurrence. Every patient included in this series was evaluated in the light of this possibility, especially when cases with positive cephalin cholesterol flocculation and a negative heterophile antibody titer were encountered. It is believed that the differentiation has been as accurate as present knowledge and the methods employed permit. The uncertainty which still exists is further evidence of the similarity which is not infrequently exhibited by these diseases. In spite of the failure to demonstrate a correlation between abnormalities of liver function and the persistence of symptoms during infectious mononucleosis, it seems reasonable to manage patients with this disease by carefully controlled activity and diet in the manner shown to be beneficial for the treatment of infectious hepatitis. Further, since the etiology of infectious mononucleosis has not been clarified, it would seem logical to employ the methods which have been successful in recognizing the specific etiology of infectious hepatitis to the study of infectious mononucleosis.

SUMMARY

The results of tests of liver function performed at random or in series during the course of infectious mononucleosis in eighty-three patients are presented. Abnormal values were obtained in seventy-five. Of the tests employed the cephalin cholesterol flocculation was positive most frequently. A value of +++ or more was obtained in

MARCH, 1949

thirty-eight of thirty-nine patients who had a series of tests. This persisted for an average of thirty days. Thymol turbidity values were 4 units or more in nineteen of twenty-nine cases (65 per cent) in which a series of tests was made. It remained positive for an average of thirty-five days. The icterus index was 10 units or more and the urobilinogen excretion abnormal in over one-third of the cases examined. Bromsulfalein retention (5 mg., thirty minute-technic) was 10 per cent or more in twenty of forty-one cases (49 per cent). The usefulness of these tests in indicating the presence of hepatitis is considered. The available evidence would seem to justify the conclusion that true hepatitis occurs in a significant proportion of all cases of infectious mononucleosis.

In this series a relapse of acute symptoms or clinical evidence of chronic liver disease was not observed. Some patients whose subsequent course is unknown had abnormal liver function tests when they were last examined. The cephalin cholesterol flocculation test was positive more uniformly than the heterophile antibody determination. When infectious hepatitis of viral etiology could be eliminated with reasonable certainty, it proved to be a valuable aid in the early diagnosis of infectious mononucleosis.

Accurate differentiation between infectious mononucleosis and infectious hepatitis of virus etiology with or without jaundice was found to be impossible in occasional cases. In agreement with the conclusions of other investigators it is suggested that patients with infectious mononucleosis should be treated in the manner known to be beneficial for the management of infectious hepatitis.

Acknowledgment: The authors are indebted to Miss Rebecca Arneson for valuable technical assistance.

REFERENCES

1. COON, H. M. and THEWLIS, E. Infectious mononucleosis. A case report. *Wisconsin M. J.*, 21: 191, 1922.
2. BALDRIDGE, C. W., ROHNER, F. J. and HANSMANN, G. H. Glandular fever (infectious mononucleosis). *Arch. Int. Med.*, 38: 413, 1926.
3. BERNSTEIN, A. Infectious mononucleosis. *Medicine*, 19: 85, 1940.
4. EPSTEIN, S. H. and DAMESHEK, W. Involvement of

- the central nervous system in a case of glandular fever. *New England J. Med.*, 205: 1238, 1931.
5. THELANDER, H. E. and SHAW, E. C. Infectious mononucleosis with special reference to cerebral complications. *Am. J. Dis. Child.*, 61: 1131, 1941.
 6. SLADE, J. DE R. Involvement of the central nervous system in infectious mononucleosis. *New England J. Med.*, 234: 753, 1946.
 7. PETERS, C. H., WIDERMANN, A., BLUMBERG, A. and RICKER, W. A., JR. Neurologic manifestations of infectious mononucleosis with special reference to the Guillain-Barré syndrome. *Arch. Int. Med.*, 80: 366, 1947.
 8. FIELD, W. W. Infectious mononucleosis with severe central nervous system involvement. *Am. J. Med.*, 4: 154, 1948.
 9. WECHSLER, H. F., ROSENBLUM, A. H. and SILLS, C. T. Infectious mononucleosis: report of an epidemic in an army post. Part I. *Ann. Int. Med.*, 25: 113, 1946.
 10. WECHSLER, H. F., ROSENBLUM, A. H. and SILLS, C. T. Infectious mononucleosis: report of an epidemic in an army post. Part II. *Ann. Int. Med.*, 25: 236, 1946.
 11. LYGT, C. E. Infectious mononucleosis. *Journal-Lancet*, 58: 91, 1938.
 12. ZIEGLER, E. E. Infectious mononucleosis: report of a fatal case with autopsy. *Arch. Path.*, 37: 196, 1944.
 13. ALLEN, F. H., JR. and KELLNER, A. Infectious mononucleosis: an autopsy report. *Am. J. Path.*, 23: 3, 1947.
 14. RICKER, W., BLUMBERG, A., PETERS, C. H. and WIDERMANN, A. The association of the Guillain-Barré syndrome with infectious mononucleosis with a report of 2 fatal cases. *Blood*, 3: 217, 1947.
 15. DAVIS, J. S., MACFEE, W., WRIGHT, M. and ALLYN, R. Rupture of the spleen in infectious mononucleosis. *Lancet*, 2: 72, 1945.
 16. VAN BEEK, S. I. and HAEX, A. H. CH. Aspiration-biopsy of the liver in infectious mononucleosis and in Besnier-Boeck-Schaumann's disease. *Acta med. Scandinav.*, 113: 125, 1943.
 17. FISHER, J. H. Visceral lesions of acute infectious mononucleosis: a report of 2 cases with fatal spontaneous rupture of the spleen. *Am. J. Path.*, 42: 651, 1946.
 18. BANG, J. and WANSCHER, O. The histopathology of the liver in infectious mononucleosis complicated by jaundice. *Acta med. Scandinav.*, 120: 437, 1945.
 19. MACKEY, R. D. and WAKEFIELD, E. G. The occurrence of abnormal lymphocytes in the blood of a patient with jaundice (infectious mononucleosis glandular fever). *Ann. Clin. Med.*, 4: 727, 1926.
 20. DOWNEY, H. and MCKINLAY, C. A. Acute lymphadenosis compared with acute lymphatic leukemia. *Ann. Int. Med.*, 32: 82, 1923.
 21. SPRING, M. Jaundice in infectious mononucleosis. *Bull. U. S. M. Dept.*, 81: 102, 1944.
 22. COHN, C. and LIDMAN, B. I. Hepatitis without jaundice in infectious mononucleosis. *J. Clin. Investigation*, 25: 145, 1946.
 23. DEMARSH, Q. B. and ALT, H. L. Hepatitis without jaundice in infectious mononucleosis. *Arch. Int. Med.*, 80: 257, 1947.
 24. GALL, E. A. Serum phosphatase and other tests of liver function in infectious mononucleosis. *Am. J. Clin. Path.*, 17: 529, 1947.
 25. EVANS, A. S. Liver involvement in infectious mononucleosis. *J. Clin. Investigation*, 27: 106, 1948.
 26. BARKER, M. H., CAPPS, R. B. and ALLEN, F. W. Acute infectious hepatitis in the Mediterranean Theater, including acute hepatitis without jaundice. *J. A. M. A.*, 128: 997, 1945.
 27. JONES, C. M. and MINOT, G. R. Infectious (catarrhal) jaundice. An attempt to establish a clinical entity. Observations on the excretion and retention of the bile pigments and on the blood. *Boston M. & S. J.*, 189: 531, 1923.
 28. DAVIDSOHN, I. Serologic diagnosis of infectious mononucleosis. *J. A. M. A.*, 108: 289, 1937.
 29. DAVIDSOHN, I. Test for infectious mononucleosis. *Am. J. Clin. Path.*, 8: 56, 1938.
 30. WALLACE, G. B. and DIAMOND, J. S. The significance of urobilinogen in urine as a test of liver function. *Arch. Int. Med.*, 35: 698, 1925.
 31. HANGER, F. M. Serological differentiation of obstructive from hepatogenous jaundice by flocculation of cephalin-cholesterol emulsions. *J. Clin. Investigation*, 18: 261, 1939.
 32. MACLAGAN, N. F. The thymol turbidity test as an indicator of liver function. *Brit. J. Exper. Path.* 25: 234, 1944.
 33. POHLE, F. J. and STEWART, J. K. The cephalin-cholesterol flocculation test as an aid in the diagnosis of hepatic disorders. *J. Clin. Investigation*, 20: 241, 1941.
 34. QUICK, A. J. On the quantitative estimation of prothrombin. *Am. J. Clin. Path.* 15: 560, 1945.
 35. COHEN, P. P. and THOMPSON, F. L. Mechanism of the thymol turbidity test. *J. Lab. & Clin. Med.*, 32: 475, 1947.
 36. KUNKEL, H. Value and limitations of the thymol turbidity test as an index of liver disease. *Am. J. Med.*, 4: 201, 1948.
 37. HANGER, F. M. Abnormalities in the globulin component of serum as demonstrated by the cephalin flocculation test. *Tr. Am. Physicians*, 60: 82, 1947.
 38. WHITE, A. and DOUGHERTY, T. F. The pituitary adrenotrophic control of the rate of release of serum globulins from lymphoid tissue. *Endocrinology*, 36: 207, 1945.
 39. WACHSTEIN, M. Alkaline phosphatase activity in normal and abnormal human blood and bone marrow cells. *J. Lab. & Clin. Med.*, 31: 1, 1946.
 40. WOODARD, H. Q. and CRAVER, L. F. Serum phosphatase in the lymphomatoid diseases. *J. Clin. Investigation*, 19: 1, 1940.
 41. WHITE, F. W., MEIKELJOHN, A. P., DEUTSCH, E. and KARK, R. A comparison of 3 urobilinogen tests in the urine (the Watson, Sparkman, and Wallace and Diamond methods) in jaundice and diseases of the liver. *Am. J. Digest. Dis.* 8: 346, 1941.
 42. HAVENS, W. P., JR. Experiment in cross immunity between infectious hepatitis and homologous serum jaundice. *Proc. Soc. Exper. Biol. & Med.*, 59: 148, 1945.
 43. ABRAMS, H. L. Infectious mononucleosis with intense jaundice of long duration. *New England J. Med.*, 238: 295, 1948.
 44. STILLERMAN, H. B. The thymol turbidity test in various diseases. *J. Lab. & Clin. Med.*, 33: 565, 1948.

Endocrinopathies Associated with Hyperostosis Frontalis Interna*

FLOYD E. HARDING, M.D.

Los Angeles, California

THICKENING of the internal table of the frontal bone occurs more frequently than is generally supposed, and associated with it there are usually some metabolic, endocrine, neuropsychiatric or hypertensive manifestations. When one or more of these abnormalities are present with hyperostosis frontalis interna, a syndrome is formed which is sometimes called "metabolic craniopathy," Morgagni syndrome or Stewart-Morel syndrome.

Although the characteristic thickening in the frontal bone had been observed in museum specimens since ancient times, and Morgagni¹ noted the syndrome of obesity, virilism and thickening of the bone in 1765, the modern concept of its clinical significance was initiated in 1928 after Stewart² reported three cases of the syndrome diagnosed at autopsy. However, the first living person with hyperostosis frontalis interna was reported by Morel³ in 1930, and only three living people with the disease^{4,5} had been reported up to 1936 when Henschen⁶ diagnosed twenty-eight cases. In 1935 to 1936 Moore⁷⁻⁹ reviewed 6,650 roentgenograms of the skull, about one-half of which were taken on females, and found that the films of 3.4 per cent of the patients showed some evidence of thickening of the inner table. He checked the case records of 193 patients, making a personal study of six patients and found that certain nervous and metabolic symptoms were more prevalent than in hospital and clinic patients in general. Since then several articles have appeared in the literature with discussions of from one to sixty-six cases.¹⁰⁻²⁷

Various theories have been advanced

regarding the cause of this condition, but none of them fits all the cases. Pituitary dysfunction, among other things, has been suspected. There is no evidence at the present time that pituitary disease produces hyperostosis and it must be stated that the etiology is unknown.

Although endocrine disease has been mentioned as being a part of the syndrome by many writers, very little detail has yet been given. The purpose of this paper is to show the frequency of endocrine abnormalities and their relationship to other findings as they were observed in our patients with hyperostosis frontalis interna. It is an analysis of ambulatory patients seeking office treatment.

ANALYSIS OF CASES

Seventeen cases were found, all in women. They were located by watching for the condition among the last 251 patients having roentgenograms made of their skulls for the endocrine department. Twenty-six females under the age of eighteen and thirty-seven males showed no evidence of the abnormality. A control group of thirty-eight non-obese females over the age of eighteen had normal-appearing skulls. Of the 150 obese women over the age of eighteen, part of whom had a psychoneurosis, seventeen or 11 per cent had some degree of hyperostosis frontalis interna. Of all women over the age of eighteen for whom films of the skull were made 9 per cent had this condition.

The diagnosis was always proved by taking x-ray pictures of the skull. In a few instances the diagnosis was made prior to seeing the films. Because of the protean

* From the Department of Endocrinology, Ross-Loos Medical Group, Los Angeles, Calif.



FIG. 1. A to D, Miss M. M., Case XI after losing weight from 210 to 160 pounds by dieting.

nature of the disease, it was difficult to make a diagnosis without the x-ray findings. (Figs. 1 to 5.)

The ages of the patients ranged from eighteen to fifty-two years. A total of eighteen children had been born to ten women. There was one single girl. The other six married women had no children.

The following diagnoses of endocrine disease were made: diabetes mellitus, two cases; myxoedema, one case; non-toxic goiter, one case; hyperthyroidism (prior to thyroidectomy), one case; secondary amenorrhea, two cases; menopause due to radium

therapy, one case; menopause due to x-ray therapy, one case; climacteric-natural, two cases; artificial menopause (surgical), four cases; sterility (anovulatory), two cases and bilateral cystic ovaries (surgical diagnosis during an appendectomy), one case.

In addition, there were two cases of probable hypothyroidism and one case of possible hypothyroidism. One patient had exophthalmos. The vaginal smears were changed by infections, previous treatment, etc., but they showed evidence of estrogen deficiency in several patients. Ten of the sugar tolerance tests showed a slight in-

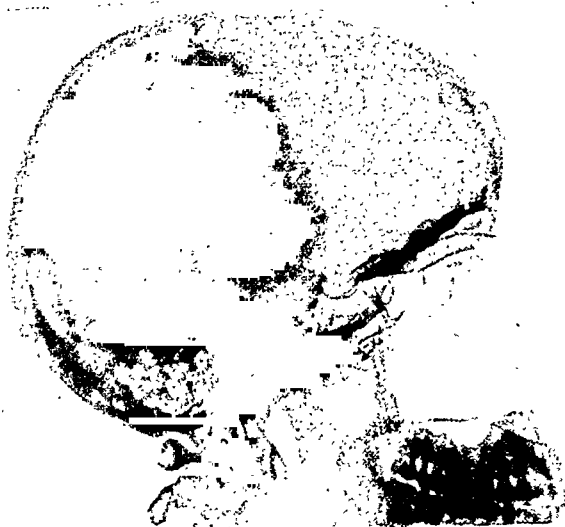


FIG. 2. Case XI; hyperostosis frontalis interna.

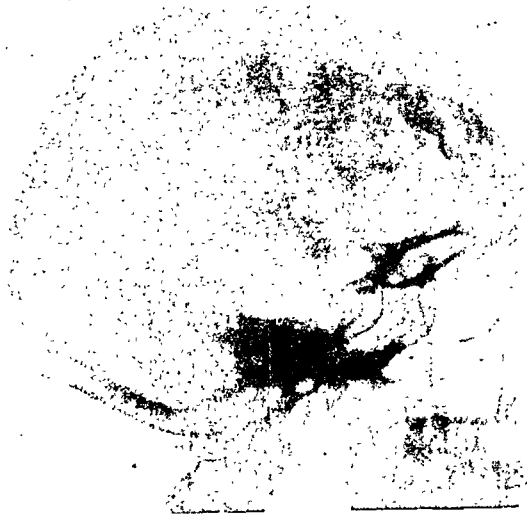


FIG. 3. Case III; hyperostosis frontalis interna.

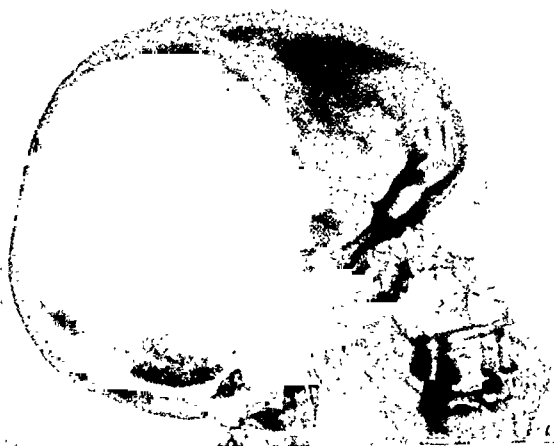


FIG. 4. Case V; hyperostosis frontalis interna.



FIG. 5. Case XIII; hyperostosis frontalis interna.

crease in the amount of blood sugar in one or more of the determinations, possibly due to a pituitary disorder, a tendency to develop diabetes mellitus, abnormal liver function or other glandular disorders. (Table I.) Some of these figures were without doubt normal as they were within the range of findings that could be normal. Two patients had sugar in their urine. Several members of the family of one of the diabetic patients had diabetes mellitus.

Numerous symptoms and signs of possible endocrine importance were noted. (Table II.) The basal metabolic rate was above plus 10 for one patient and below minus 10 for seven. The clinoid processes of the sella turcica of four patients were bridged. A hysterectomy had been per-

formed on four patients. The height ranged from 59 to 68 inches and averaged 63 inches. The weight varied from 109 pounds to 280 pounds. The weight was normal for the height and age in only three patients, but they had dieted strictly for years to keep their weight down. The other fourteen women had 709 pounds of excess weight, averaging 50 pounds per patient. A record of family obesity was found in ten case histories. The blood pressure was above normal in seven patients. The blood calcium was normal for the eight patients tested. Four blood cholesterol tests were high enough to be considered in a diagnosis of

mild hypothyroidism, i. e., 198, 210, 210 and 270. The only test that was definitely elevated, however, was the latter one. Blue striae were found on two patients, suggesting pituitary involvement. Eight patients were no longer menstruating, one having

cardia, paresthesias, flatulence, epigastric distress, mastalgia, psychalgia, nocturia, frigidity, difficulty in thinking and concentrating, indecision, pruritus of the labia majora, nightmares, phobias and tinnitus. Other unpleasant symptoms were described

TABLE I
BLOOD CHEMISTRY: SUGAR TOLERANCE* AND OTHER TESTS

Case No.	Name	Fasting Blood Sugar	One-half Hr.	One Hr.	Two Hr.	Sugar in the Urine	Cholesterol†	Calcium‡
I	C. S.	207	2 plus	176	11
II	B. F.	134	...	170	165	3 plus-1 hour	150	
III	B. J.	Negative		
IV	F. C.	94	111	118	108	Negative	141	12
V	S. M.	101	185	175	133	Negative	270	
VI	M. W.	104	158	158	94	Negative		
VII	H. C.	115	149	143	134	Negative	132	11.5
VIII	F. B.	103	122	111	101	Negative	210	11
IX	B. B.	210	4 plus	150	
X	I. S.	143	221	184	164	Negative	138	11
XI	M. M.	92	117	127	104	Negative	129	
XII	E. B.	103	155	161	128	1 plus-1 hour	165	10
XIII	L. B.	126	134	125	123	Negative	147	
XIV	G. R.	104	150	158	137	Negative	198	
XV	J. T.	93	151	108	86	Negative	210	
XVI	M. I.	109	141	109	...	Negative	180	12
XVII	E. A.	103	158	131	85	Negative	135	11

* The Folin-Wu method.

† Reported as mg. in 100 cc. blood plasma.

‡ Reported as mg. in 100 cc. blood serum.

stopped at the age of nineteen. This latter patient is now fifty years old. Five patients menstruated every twenty-eight days, whereas three had late periods and one bled semimonthly. Eight patients had dry skins but one woman had profuse perspiration. Seven patients had dry hair and five had brittle nails. Eleven patients were bothered by hot flushes. Six patients complained of feeling too cold. Thirteen patients had some hirsutism although in five it was slight. Six patients had had dysmenorrhea during the menacme.

Other symptoms are listed in Table III. Most of the patients were forgetful and some of them had trouble thinking of the right word to say. Many complained of various symptoms, such as palpitation, dyspnea, polyphagia, somnolence, insomnia, back-ache, precordial pain, scotomas, tachy-

by the patients in the following manner: "difficult to get a satisfying breath," "legs cramp," "something snaps and I feel as if I am on a different plane," "jerking of muscles all over the body," "spells of anger," "quiver all over," "lost strength in the left arm" and "a burning spot the size of a dollar on each buttock."

The following diseases were also diagnosed: asthma, allergic rhinitis, urticaria, vitiligo, epilepsy, secondary anemia, neurodermatitis and pseudocyesis.

Most of the patients were psychoneurotics and had had nervous breakdowns. There was a high rate of morbidity with considerable remission and exacerbation of the symptoms.

TREATMENT

No effective treatment is known for the hyperostosis. For diseases associated with it

specific treatment was frequently given. For instance, myxoedema and symptoms of hypothyroidism responded to thyroid extract. There was great improvement with complete relief of hot flushes in the menopausal or estrogen-deficient patient when

the caloric content was decreased. A minimum amount of protein was allowed. This limited choice of foods resulted in a diet consisting largely of fruits and vegetables, the sugar content of which stimulated the pancreas to produce more insulin. The benefit

TABLE II
CLINICAL AND LABORATORY DATA OF POSSIBLE ENDOCRINE IMPORTANCE

Case No.	Age	Weight	Height in Inches	Blood Pressure	Children	Menses	Surgery or Therapy	Vaginal Smears		Hot Flushes	Too Cold	Dry Skin	Dry Hair	Brittle Nails	Basal Metabolic Rate	Goiter	Hirsutism	Hyperostosis Frontalis Interna
								G	C									
I	45	270	67	166/100	3	0	X I OY	+	+	++	+	+	+	+	+18	0	+	+
II	37	154	62	130/96	2	R	+++	+++	0	0	0	0	0	-14	0	+	+
III	36	176	60	166/94	1	R	++++	+++	0	0	+	+	0	-5	0	+	+++
IV	50	280	67	154/110	1	0	+	++	+	0	0	0	0	-25	0	++	++
V	38	109	62	114/64	0	0	2 OY H	++	++	++	0	0	+	0	-13	0	0	++
VI	40	122	62	130/90	1	I	+++	+++	+	0	0	0	0	-1	0	+	+
VII	30	164	67	120/70	0	I	+	++	0	+	0	-11	0	0	+++
VIII	43	168	60	120/70	0	0	++	0	0	0	0	-16	0	0	+
IX	51	160	59	208/100	3	0	Ra	++	0	0	0	+	-4	0	++	++
X	33	172	62	118/84	2	R	+	++	0	0	0	0	0	-11	0	++	+
XI	18	210	63	104/64	0	I	0	+	+	0	+	-18	0	++	++
XII	52	245	68	164/116	2	R	+	+	0	0	+	0	0	-4	0	0	+
XIII	31	148	63	120/74	0	R	+++	+++	0	+	+	+	0	-26	0	++	++
XIV	51	162	60	125/82	1	0	H	++	++	0	+	++	++	+	+9	T	+	++
XV	46	165	67	150/100	0	0	H	++	+++	+	0	+	0	+	-5	+	++	+
XVI	38	164	61	222/120	0	I	+++	++	+	++	++	++	0	-1	0	+	++
XVII	43	137	61	110/70	2	0	H	++	++	+	0	0	0	0	+1	0	+	+

R—Regular

I—Irrregular or late

X—X-ray therapy to ovaries

Ra—Radium therapy intrauterine

I OY and 2 OY—Unilateral and bilateral oophorectomy

H—Hysterectomy

G—Glycogen in vaginal smears

C—Cornification of vaginal cells

+—Slight cornification of cells

++++—Complete cornification of cells

T—Thyroidectomy

hexestrol or conjugated estrogens—equine were given in effective oral doses. Diabetes mellitus was controlled by insulin and hyperthyroidism was corrected by thyroidectomy. Obesity responded to a low caloric diet even though it appeared to be on an endogenous basis. The low sugar tolerance, as shown by a greater than average increase in blood sugar, was improved by a low fat diet and if the patient was also overweight

obtained with this method was demonstrated by Case XII. Before treatment this patient had the following sugar tolerance: fasting, 103; one-half-hour, 155; one-hour, 161 and two-hour, 128 with some sugar in the first and second-hour urine specimens. After treatment there was less sugar: fasting, 109; one-half-hour, 138; one-hour, 126; three-hour, 63 and five-hour, 72 with the urine test negative for sugar. Actually the three-

hour specimen was a little low, probably due to overproduction of insulin. In Case VII there was a response similar to that in Case XII with the following sugar tolerance before treatment: fasting, 115; one-half-hour, 149; one-hour, 143 and two-hour, 134.

TABLE III
SYMPTOMS

Symptom	No. of Patients
Nervousness.....	16
Asthenia.....	16
Weakness.....	15
Dizziness.....	15
Headache.....	14
Mental depression.....	13
Poor vision.....	12
Giddiness.....	11
Diplopia.....	3

After treatment the blood sugar readings were lower: fasting, 92; one-half-hour, 112; one-hour, 120; three-hour, 96 and five-hour, 82.

Some of the patients required symptomatic treatment. Phenobarbital allayed the nervousness and mental depression. Gynergen was helpful for the headaches.

It was explained that many of the symptoms were due to the accompanying neurosis and, unless severe, should be ignored. Some practical advice was given concerning the psychoneurosis.

COMMENT

Morbidity, headache, forgetfulness, asthenia, vertigo, obesity, poor vision and either psychoneurosis or psychosis occur too frequently with hyperostosis frontalis interna to be coincidental. The fact that this condition is found almost exclusively in the female is also important. In our series of cases there was a high rate of endocrine disorders which, of course, may have been coincidental in the small number of patients. However, the findings are important in that they show the need for making complete endocrine studies on these patients as well as a very thorough history and general examination.

A study of the literature as well as the present series of cases convinces one that these patients have many disturbances of a varied nature. There is some similarity in

the group as a whole but considerable individual difference. Possibly the cause of metabolic craniopathy produces changes in different parts of the system and the symptoms vary according to the parts involved. For instance, there are areas of atrophy in the frontal lobes and sometimes other parts of the brain. This degeneration occurs mostly in the so-called "silent area," and the bone protrudes into the involved parts. The variation in the amount and location of cerebral involvement may determine to some extent the amount of forgetfulness, headache, etc. The disease may occasionally cause trouble in the hypothalamus with resultant obesity and/or primary pituitary disturbance with secondary thyroid, ovarian or adrenal involvement.

It has been stated that the pituitary gland may be responsible for this disease. This idea developed, at least in part, from the opinion previously believed but now thought to be incorrect that obesity of the type seen in these patients is due to a disturbance in pituitary function. It seems improbable that hyperostosis frontalis interna is caused by any type of abnormal pituitary function as it is not consistently found with any known type of pituitary disease.

There is a similarity in the appearance of these patients because the obesity is usually of the rhizomelic type. The pictures shown in the literature are mainly of this type. However, Tager et al.¹⁴ found the weight to be above normal in only twenty-six of sixty-six patients studied by them. Nevertheless, even in their group of patients the percentage of obesity was greater than in the general population.

It is reported that hyperostosis frontalis interna is sometimes found in normal asymptomatic individuals. Possibly the bony changes have preceded the appearance of symptoms. According to the literature available,¹⁻²⁷ the incidence of this condition in otherwise normal women is quite low. None of our patients could be classed as normal.

A thorough study of the patient with the consultation of specialists for diagnosis of

definite abnormalities will avoid treatment for diseases not present. A careful explanation of the condition will prevent the patient from continuously seeking new remedies from numerous doctors.

SUMMARY

The findings in seventeen women with hyperostosis frontalis interna have been tabulated and discussed. Evidence of some endocrine abnormality was frequently found but was possibly coincidental. There was great similarity of body build and symptomatology in this group of patients. As abnormal findings were numerous thorough laboratory study and detailed physical examination were essential; consultations with other specialists were frequently advisable.

Frontal headache, asthenia, forgetfulness, vertigo, nervousness, obesity and poor vision were rather characteristic of this group. There was a high degree of morbidity with frequent remission and exacerbation of symptoms.

No cause was found for this disease. It was limited almost entirely to the adult female. Some of the symptoms were probably due to cerebral atrophy.

Useful hormonal, dietary and symptomatic treatment was discussed.

REFERENCES

- MORGAGNI, J. B. De Sedibus et Causis Morborum. 27: 2, 1765.
- STEWART, R. M. Localized cranial hyperostosis in the insane. *J. Neurol. & Psychopath.*, 8: 321, 1928.
- MOREL, F. L'hyperostose Frontale Interne. Syndrome de l'Hyperostose Frontale Interne avec Adipose et Troubles Cerebraux. Paris, 1930. Gaston Doin et Cie.
- VAN BOGAERT, L. Le syndrome de l'hyperostose frontale interne chez une malade presentant par ailleurs une cécité psychique par hémianopsie double. *J. Neurol. et de Psychiat.*, 30: 502, 1930.
- SCHIFF, P. and TRELLES, J. O. Syndrome de Stewart-Morel. *Encéphale*, 26: 768, 1931.
- HENSCHEN, F. Morgagni syndrome. *Hygieia*, 98: 65, 1936.
- MOORE, S. Hyperostosis frontalis interna. A preliminary study. *Surg., Gynec. & Obst.*, 61: 345, 1935.
- MOORE, S. Metabolic craniopathy. *Am. J. Roentgenol.*, 35: 30, 1936.
- MOORE, S. Calvarial hyperostosis and accompanying symptom complex. *Arch. Neurol. & Psychiat.*, 35: 975, 1936.
- PERKINS, O. C. and BIGLAN, A. M. Hyperostosis frontalis interna. Review of the literature. *Psychiatric Quart.*, 12: 341, 1938.
- CARR, A. D. Neuropsychiatric syndromes associated with hyperostosis frontalis interna. Preliminary report. *Arch. Neurol. & Psychiat.*, 35: 982, 1936.
- KNIES, P. T. and LE FEVER, H. E. Metabolic craniopathy. Hyperostosis frontalis interna. *Ann. Int. Med.*, 14: 1858, 1941.
- ANDREWS, C. T. Hyperostosis frontalis interna. *Brit. M. J.*, 2: 185, 1942.
- TAGER, B. N., SHELTON, E. K. and MATZEN, W. C. Hyperostosis calverii interna. Its clinical significance. *California & West. Med.*, 51: 384, 1939.
- REIDER, N. Hyperostosis frontalis interna and degenerative brain disease. *J. Mt. Sinai Hosp.*, 5: 511, 1938.
- WILLIAMS, C. L. Hyperostosis of the calvarium. *J. Indiana M. A.*, 34: 361, 1941.
- ROGER, A. A. The internal frontal hyperostosis syndrome. *Canad. M. A. J.*, 38: 129, 1938.
- GOLLAN, L. N. A case of hyperostosis frontalis interna. *M. J. Australia*, 1: 23, 1939.
- BRAUNS, W. H. Hyperostosis frontalis interna. *Bull. New England M. Center*, 6: 267, 1944.
- ELDRIDGE, W. W. and HOLM, G. A. The incidence of hyperostosis frontalis interna in female patients admitted to a mental hospital. *Am. J. Roentgenol.*, 43: 356, 1940.
- TITCHE, L. L. Cerebrospinal rhinorrhea. Report of a case presenting hyperostosis frontalis interna. *Ann. Otol., Rhin. & Laryng.*, 50: 554, 1941.
- MCGAVACK, T. H. and REINSTEIN, H. Brachydactyly, polyphalangism, and brachymetapodism in a moronic individual with microcephaly, internal frontal hyperostosis, and endogenous obesity. *Am. J. Roentgenol.*, 45: 55, 1941.
- FAGIN, I. D. Dystrophia myotonica. Report of two cases with associated hyperostosis frontalis interna in one. *J. Michigan M. Soc.*, 45: 500, 1946.
- GILBERT, J. P. Stewart-Morel syndrome or syndrome of internal frontal hyperostosis. *J. Tennessee M. A.*, 35: 176, 1942.
- GERUNDO, M. and HELWIG, G. F. Morgagni's syndrome. Hyperostosis frontalis interna. *M. Rec.*, 156: 31, 1943.
- RUCH, W. A. Hyperostosis frontalis interna accompanying pregnancy. Case report. *Memphis M. J.*, 17: 195, 1942.
- GROLLMAN, A. and ROUSSEAU, J. P. Metabolic craniopathy. A clinical and roentgenologic study of so-called hyperostosis frontalis interna. *J. A. M. A.*, 126: 213, 1944.

Subacute Bacterial Endocarditis*

RUBEN SNYDERMAN, M.D. and JAMES S. TIPPING, M.D.

Pittsburgh, Pennsylvania

WITH the advent of the use of penicillin in the treatment of bacterial infections, a new era began in medicine. Subacute bacterial endocarditis, which was more than 99 per cent fatal only a few years ago, can now be cured in a large percentage of cases.

were considered in this series. Other organisms can cause subacute bacterial endocarditis but for strict clinical accuracy two cured cases of endocarditis due to staphylococci have been eliminated.

Six females and four males were treated, ranging in age from sixteen to sixty-one

TABLE I
SUBACUTE BACTERIAL ENDOCARDITIS

Case	Age	Sex	Valve Involved	Probable Precipitating Factor	Organism	Required Effective Penicillin Dose	Total Penicillin	Complications	Hospital Days	Previous Treatment
1	32	F	Mitral	Rheumatic flare-up	<i>Streptococcus non-hemolyticus (ignavus)</i>	100,000 units every 3 hr.	31,000,000	None	45	None
2	59	M	Mitral	?	<i>Streptococcus non-hemolyticus</i>	75,000 units every 3 hr.	32,950,000	Embolus to central retinal artery, blindness	39	None
3	19	M	Mitral and aortic	Boil on face	<i>Streptococcus non-hemolyticus</i>	75,000 units every 3 hr.	16,000,000	None	46	None
4	16	F	Mitral	Respiratory infection	<i>Streptococcus non-hemolyticus (mitis)</i>	200,000 units every 2 hr.	84,100,000	Cerebral embolus, right hemiplegia	67	None
5	17	F	Congenital defect	Tooth extraction	<i>Streptococcus non-hemolyticus (salivarius)</i>	200,000 units every 3 hr.	49,550,000	Multiple pulmonary emboli	52	None
6	23	F	Aortic and mitral	Respiratory infection	<i>Streptococcus non-hemolyticus (mitis)</i>	100,000 units every 3 hr.	20,750,000	Emboli to fingers	49	Yes
7	52	M	Aortic and mitral	Abscess of teeth	<i>Streptococcus non-hemolyticus (mitis)</i>	100,000 units every 3 hr.	41,800,000	Congestive heart failure	68	None
8	52	M	Mitral	Tooth extraction	<i>Streptococcus non-hemolyticus (salivarius)</i>	100,000 units every 3 hr.	38,400,000	Emboli to fingers, toes, scotomata in visual field	62	Yes
9	27	F	Aortic and mitral	Tooth extraction	<i>Streptococcus non-hemolyticus</i>	200,000 units every 3 hr.	50,000,000	None	48	None
10	61	F	Mitral	Tooth extraction	<i>Streptococcus non-hemolyticus (mitis)</i>	50,000 units every 3 hr.	10,950,000	None	38	None

We wish to add to the literature our own experience in the treatment of all the proven cases of subacute bacterial endocarditis admitted to the Presbyterian and Woman's Hospitals for the year 1946. (Table I.) These cases comprise ten patients, all of whom obtained clinical cures and continued to have negative blood cultures since their discharge from the hospital. Only those patients with positive blood cultures for the non-hemolytic streptococcus

years. Six patients, five of whom were females, were in the age group from sixteen to thirty-two. The remaining patients were ages fifty-two, fifty-two, fifty-four and sixty-one, respectively, three of whom were males. With rare exceptions, subacute bacterial endocarditis occurs in patients with pre-existing valvular or congenital heart disease. Only three of the ten patients gave no history of previous heart disease. One of these three, however, gave a history of

* From the Department of Medicine, Presbyterian and Woman's Hospitals of the University of Pittsburgh, School of Medicine, Pittsburgh, Pa.

scarlet fever and "growing pains." Upon admission this patient had a rough, loud systolic murmur of mitral insufficiency. One patient had been a "blue baby" and had a definite diagnosis of heart disease made at the age of six years. The oldest patient, age sixty-one, had influenza in 1918 and had known of her heart murmur since that time although she remained symptom-free until the present illness. Another patient, age fifty-two, with mitral insufficiency first learned of his heart murmur at the age of forty. He had no definite rheumatic history but likewise had "flu" in 1918. One patient had mitral valvular disease for ten years and had taken digitalis during this entire period but had no definite rheumatic history. Two of the remaining patients, ages nineteen and twenty-three, had recurrent attacks of rheumatic fever. The last patient, aged fifty-two, had rheumatic fever as a young adult and was told he had an enlarged heart at the age of thirty.

Valvular defects in this series were found in five patients in whom only the mitral valve was diseased. Four patients had lesions involving the mitral and aortic valves; one had a congenital defect believed to be a patent ductus arteriosus.

With the predisposing factor of chronic valvular heart disease or congenital heart disease, the precipitating factor in the actual pathogenesis of subacute bacterial endocarditis is the presence of bacteremia which permits the bacteria to localize on the defective valve or congenital defect. Asymptomatic bacteremias have been proven to occur more frequently than was previously believed. It has been demonstrated that transient asymptomatic bacteremias occur after tooth extraction or dental manipulation done during the repair of teeth. Less common bacteremias that are asymptomatic occur after tonsillectomy and other operative procedures. Many patients with subacute bacterial endocarditis gave a history of recent simple respiratory infections. In this series of ten patients five had dental work with tooth extraction just prior to the onset of their illness. One had a history of

a "boil" on the face and "sinus trouble." Two had upper respiratory infections. One had a chronic cough and an episode of gall-bladder colic with transient jaundice prior to the onset of his illness. One patient gave a history suggestive of a recurrence of rheumatic fever with polyarthrititis.

The earliest symptoms were those of a non-specific low grade infection. They complained of malaise, weakness, low grade remittent fever, chilly sensations and sweating which occurred most frequently at night. Cough, pleurisy and pains in the joints and muscles were also frequent complaints. Later in the course of the illness they developed symptoms produced by the embolic phenomena, such as sore fingers and toes with splinter hemorrhages or development of a blind spot in the visual field. The longest duration of symptoms before admission to the hospital was three months. The average was two to three weeks. Because of the vagueness and variability of symptoms and the insidious onset of this disease, it is essential to obtain repeated blood cultures in any patient with chronic valvular or congenital heart disease who presents himself with fever or unexplained symptoms.

The absolute diagnosis of subacute bacterial endocarditis can only be made in the presence of positive blood cultures. Before treatment is instituted it is essential to obtain positive cultures since it is usually impossible to obtain positive cultures while the patient is receiving penicillin even with penicillinase in the culture media. Rational treatment requires a knowledge of the organism and its sensitivity to the therapeutic agent. If the sensitivity of the organism to penicillin is known, one has some idea of the prognosis and the probable dosage required to achieve a cure. An organism highly resistant to penicillin will be difficult to eradicate even with large doses of penicillin, and the use of sulfonamide drugs combined with penicillin must be considered. If the individual has received penicillin or a sulfonamide drug prior to admission to the hospital, it may require

several days for the blood concentration to fall to a level which will permit the organism to grow. At least two cultures should be taken each day, one in the morning and one in the afternoon. If a marked elevation of temperature or an embolic phenomenon occurs, one should obtain a blood culture at such a time. Cultures should be taken aerobically and anaerobically since many of these organisms are micro-aerophils and will grow only in an atmosphere of reduced oxygen tension. Frequently the explanation for failure to obtain positive cultures is the fact that the organism must be grown anaerobically and only aerobic cultures were made. With a history of the use of a sulfonamide preparation or the use of penicillin, para-aminobenzoic acid or penicillinase, or both, must be incorporated in the media. The colony count on the pour plate should be done since it is of some value in estimating the severity of the infection.

Most of the patients in this series were started on an initial regimen of 50,000 units of penicillin every three hours, but in all but one the dosage had to be increased during the course of treatment. Two patients had the dosage increased to 75,000 units every third hour; four eventually received 100,000 units every third hour and three received 200,000 units every three hours. (One of the latter group actually received 200,000 units every two hours.) The dosage was increased due to persistence of fever, the report of persistently positive blood cultures, the presence of blood penicillin levels that were too low to inhibit growth of the particular organism involved or the occurrence of embolic phenomena. Several patients infected with resistant organisms during portions of their treatment were given bolstering doses of penicillin several times daily in the form of penicillin in oil and beeswax (300,000 units twice daily) or simply additional intramuscular injections of 200,000 units in addition to the regularly scheduled doses. The smallest total dosage used was 10,950,000 units and the largest dosage was 84,000,000 units, the

average dosage being 38,000,000 units. The large dose of 84,000,000 units was used in a girl aged sixteen who had an infection with a resistant organism and who during her illness developed a cerebral embolus.

The sensitivity of the organism to penicillin was variable. The least resistant organism encountered in this series required .625 units per cc. of culture medium for inhibition of growth. This level was easily achieved in the patient's serum. Some of the organisms encountered, especially in those who had probably been treated with inadequate doses of penicillin, developed such resistance that they continued to grow in culture media containing 20 units penicillin per cc. Although serum levels of this height never were maintained with doses of penicillin as just described (organisms continued to grow in undiluted serum samples taken midway between injections of penicillin), two patients infected with these penicillin resistant strains achieved clinical and laboratory cures.

Hospitalization of these patients averaged 51.4 days with the shortest period of hospital stay being thirty-eight days and the longest sixty-eight days.

It has been difficult in the treatment of these patients to decide when penicillin can be safely stopped. No absolute rules can be laid down and probably what one must rely upon is clinical judgment. Criteria for cure have yet to be established. However, one may arbitrarily say that these patients should receive treatment for at least a two-week period after they have become afebrile. Blood culture (with penicillinase) should remain negative and the erythrocyte sedimentation rate should be either normal or show a definite tendency in that direction. It is recommended that blood cultures should be taken at monthly intervals for a period of one year since a persistently negative culture is the proof of cure.

We have chosen the intermittent intramuscular method of administration as the most practical for routine hospital use. Either crystalline penicillin may be used or

the more slowly absorbed procaine penicillin preparations.

Some disadvantages of the continuous intravenous method are: (1) It is technically difficult to maintain. (2) The requirement of relatively large quantities of intravenous fluids over many days which may disturb the fluid and electrolyte balance of the cardiac patient who is obviously most intolerant to these changes and who can readily develop congestive failure. (3) The possibility of phlebothrombosis is great with intravenous therapy and this is an increased hazard to the bedridden patient. (4) Non-specific pyrogen febrile reactions may occur and may be difficult to differentiate from an exacerbation of the disease itself.

Technical difficulties in use of continuous intramuscular penicillin are such that there is no advantage over intermittent administration, especially in view of the now available purified crystalline forms that may even be given subcutaneously with small hypodermic needles.

Anticoagulants were not used in this series of cases for several reasons: The increased tendency to hemorrhage induced by heparin and dicumarol is an additional danger to the patient, and their use is not justified in view of recent reports in the literature which have cast doubt upon their value in the therapy of subacute bacterial endocarditis. Since heparin must be given either by frequent intravenous injection or by the rather painful intramuscular injection of Pitkin's menstruum, it adds a burden to a patient already receiving numerous injections of penicillin. Anticoagulant therapy also adds to the cost and inconvenience, both to the patient and to the laboratory as daily prothrombin times and frequent urinalyses are required. Prolonged heparin therapy is expensive and this money may be used to a better advantage in providing more prolonged treatment with penicillin.

Common complications may be divided into three groups: i.e., those resulting from emboli, congestive heart failure and rupture

of a heart valve. Perhaps one should also include complicating factors such as allergy to the therapeutic agent as manifest by fever and skin rashes. This is especially true of the urticarial type. Of the embolic phenomena perhaps the most serious complications are emboli to brain, eyes and mesenteric vessels. Now that the survival period has become longer, more cases of congestive failure have become evident. This seldom was seen previously since patients succumbed to the toxemia early in the disease. In our series there have been complications in five of the patients. They were cerebral embolus with hemiplegia, embolus to the central retinal artery with resulting blindness, appearance of a scotoma in the visual field, congestive heart failure and one case of urticaria secondary to penicillin therapy. This latter condition was remedied by a change in the brand of penicillin.

Any known foci of infection are best removed during the course of treatment when blood levels of penicillin are at a maximum. However, removal of foci of infection is not recommended until control of the disease has been accomplished. Ideally this should be done toward the latter part of treatment, at which time there is some hope that the bacteria at the focus itself may possibly have been eradicated by prolonged high concentration of the drug. Every effort should be made to prevent subacute bacterial endocarditis which is so damaging to the health of the victim and which produces such great economic loss. Although little can be done to eliminate the predisposing factor (i.e., valvular damage from rheumatic fever or a congenital defect), it is believed that in many cases it can be prevented by watching for foci of infection and, particularly, by use of sulfonamide drugs or preferably penicillin before, during and after removal of these foci. This is especially true in manipulation or extraction of teeth as is shown by the fact that five of the ten patients herein reported had had recent previous dental work. On the ward service of this hospital those patients who have infected teeth with or without

cardiac lesions, or any patient with a cardiac lesions as just described is given penicillin for at least a twelve-hour period before and forty-eight hours after dental extraction usually in doses of 20,000 units every three hours. Sulfadiazine also may be used providing an adequate blood level has been reached prior to the time of removal of the focus and that it is maintained for a period of at least forty-eight hours thereafter. Penicillin in oil and beeswax may be used giving 300,000 units the day before, the day of and the day following the operative procedure.

SUMMARY

1. In the year 1946 ten patients with subacute bacterial endocarditis due to non-hemolytic streptococcus were admitted to this hospital. All have achieved cures with the use of penicillin.

2. Five of the ten patients had had recent dental work prior to onset of the illness which probably precipitated the infection.

3. Treatment should not be started until a positive blood culture is obtained and the organism isolated for further study.

4. Both aerobic and anaerobic blood cultures should be made.

5. Patients should be started on a minimum of 75,000 to 100,000 units of penicillin every three hours since in this series smaller doses were found inadequate. The minimum daily dose that should be administered is at least 600,000 units of penicillin per twenty-four hours. This also may be given in the form of slowly absorbable, procaine penicillin preparations.

6. Valuable information can be obtained by checking blood penicillin levels and penicillin resistance of the organism.

7. The intermittent intramuscular method of administration of penicillin is the preferred method.

8. It is best that foci of infection should

be removed toward the latter part of treatment when the penicillin blood level is still high.

9. Prophylactically, patients with chronic valvular heart disease or congenital heart disease should be treated with penicillin or a sulfonamide preparation before, during and after removal of foci of infection in order to avoid subacute bacterial endocarditis.

REFERENCES

1. LIBMAN, E. and FRIEDBERG, C. K. Subacute Bacterial Endocarditis. New York, 1941. Oxford University Press.
2. WHITE, P. D., MATHEWS, M. W. and EVANS, E. Notes on the treatment of subacute bacterial endocarditis encountered in 88 cases at the Massachusetts General Hospital during the six year period 1939 to 1944. *Ann. Int. Med.*, 22: 61-74, 1945.
3. OKELL, C. C. and ELLIOT, S. D. Bacteremia and oral sepsis with special reference to etiology of subacute bacterial endocarditis. *Lancet*, 2: 869-872, 1935.
4. NORTHROP, P. M. and CROWLEY, M. C. Further studies on the effects of the prophylactic use of sulfathiazole and sulfamerazine on bacteremia following extraction of teeth. *J. Oral Surg.*, 2: 134-140, 1944.
5. ANDERSON, D. G. and KEEFER, C. S. The treatment of nonhemolytic streptococcus subacute bacterial endocarditis with penicillin. *M. Clin. North America*, 29: 1129, 1945.
6. GOERNER, J. R. and BLAKE, F. G. Treatment of subacute bacterial endocarditis with penicillin: report of cases treated without anticoagulant agents. *Ann. Int. Med.*, 23: 491, 1945.
7. BIGGER, J. W. Synergistic action of penicillin and sulphonamides. *Lancet*, 2: 142, 1944.
8. LOEWE, L. The combined use of penicillin and heparin in the treatment of subacute bacterial endocarditis. *Canad. M. A. J.*, 52: 1-14, 1945.
9. MASSEL, F. and JONES, T. DUCKETT. Subacute bacterial endocarditis. *New England J. Med.*, 235: 605-608, 1946.
10. PRIEST, WALTER S., SMITH, JACQUES M. and MCGEE, CHARLES J. The effects of anticoagulants on the penicillin therapy and the pathologic lesion of subacute bacterial endocarditis. *New England J. Med.*, 235: 699-706, 1946.
11. FLIPPIN, HARRISON F., MAYLOCK, ROBERT L. and WHITE, WILLIAM L. The treatment of bacterial endocarditis. *M. Clin. North America*, 30: 1233, 1946.
12. SEABURY, JOHN H. Subacute bacterial endocarditis. *Arch. Int. Med.*, 79: 1-21, 1947.

Epidemiology of Syphilis*

THEODORE J. BAUER, M.D. and ALBERT P. ISKRANT, M.A.

Washington, D. C.

CASE finding is of first importance in syphilis control. It is the process which must be fulfilled before treatment which leads to the ultimate objective, control, can be effected.

Three factors have been largely responsible for the present emphasis on syphilis case finding: (1) The strengthening of national venereal disease control through the 1938 amendment to the Venereal Disease Control Act, (2) the acceleration of control efforts brought about by the exigencies of the war years and (3) the development of intensive syphilotherapy. This last factor had a dual effect upon case finding. Effective, rapid treatment brought about a realization of the shortcomings of case finding, and at the same time it freed much personnel time heretofore required for the administration of treatment and case holding.

Essentially, there are only three basic methods among many variations of case finding:

Screen Examination. Screen examination is that process whereby physical or laboratory examination for the presence of venereal disease is given an individual because he is a member of a group, all of whom are to be examined because they belong to that group. Prenatal or premarital testing, community-wide blood testing and routine examination among hospital admissions are examples of such groups.

Public Information. Public information includes the planned use of mass informational media, such as newspapers, radio broadcasts, posters and pamphlets, to disseminate among the general population or groups of the population specific facts

regarding the nature of venereal disease. These facts include the means of transmission of venereal disease, symptoms, possible consequences if untreated and the methods and availability of diagnosis and treatment. Discussion meetings, lectures before groups and similar devices for reaching smaller selected groups are also used. The objective of public information is to induce those who suspect infection to seek diagnosis and also to advise how infection may be avoided.

Contact Investigation. This includes all the activities involved in obtaining from each person in whom a diagnosis of venereal disease is established the information necessary to identify and locate persons who may have infected the patient or may have been infected by the patient and in finding these contacts and inducing them to accept examination and, if necessary, treatment. This process is also called "contact tracing," "the direct epidemiologic approach," "shoe leather epidemiology" and sometimes just "epidemiology."

Contact investigation can be used at any time in any area, and through this method syphilis can be found in the early stages even when symptoms are fleeting or unrecognized by the infected person. Theoretically, the investigation of persons known to have been exposed to syphilitic individuals during their infectious period produces the most direct and profitable results of all case finding technics in terms of finding early syphilis. It brings about the examination of contacts when they are infectious or potentially so and thus prevents further spread of the disease. Speed, therefore, is essential in contact investigation if the potentialities of this method are to be realized to the fullest advantage.

* From the Venereal Disease Division, Public Health Service, Federal Security Agency, Bethesda, Md.
MARCH, 1949

The first step in the investigation process is interviewing the diagnosed patient to obtain identifying information regarding his contacts. The success of the entire process depends upon this interview. In order to break chains of infection new cases of syphilis must be located and brought to treatment before the infection spreads in an ever widening circle.

The source of infection is often emphasized in discussions on contact investigation. Many venereal disease records and reports carry space for insertion of the name of the source. Identifying and locating the so-called source is important, but overemphasis on this factor has frequently resulted in too little attention being given to the so-called "spread" contacts. Furthermore, it may be impossible and even undesirable to differentiate the source of infection from other contacts. It is probable that latent syphilis would be the diagnosis in a source contact. Those persons to whom the patient may have transmitted the disease are far more likely to be in the open lesion or pre-lesion stage of the disease when examined. Therefore, interviewers should not concentrate their efforts on determining the source of infection but should obtain the names of all persons exposed to the patient within a period when it might reasonably be expected that he was in an infectious period.

Because of the sexual intimacy through which venereal disease is usually acquired, it is sometimes assumed that there may be considerable reluctance on the part of the venereal disease patient to give a physician, health officer or interviewer the information necessary for effective contact investigation. Thus, interviewing for contacts is not emphasized in some clinics and physicians' offices to the same degree that it is for diseases such as smallpox and diphtheria.

In recent years evidence has shown that the venereal disease patient is more willing to cooperate than had been realized. Large groups of patients are willing to give the names of their sex partners, and in many health departments the average is between

three and four contacts per patient. Such success, of course, requires skillful and adequate personnel. Patients will respond to a clear and sympathetic explanation of the need for their cooperation and will demonstrate an active interest in supplying information and assistance. When a friendly, non-censorious approach is used in the interview and when the purpose of the process is discussed with the patient, the average number of contacts obtained is approximately four per patient.

Many states and cities prepare special tabulations on contact investigation which are made available to the Public Health Service for comparative analysis. One of the statistics calculated from these data is the contact index which is the ratio of contacts reported per patient diagnosed. From January, 1944 to December, 1947 the average of all areas for named contacts of primary and secondary syphilis increased from 1.25 per patient to 2.07 per patient. During the six-month period of July to December, 1947 the average number of contacts reported per patient with open lesion syphilis was 2.07. The ratio varied from .43 in one area to 4.14 in another. In a special study conducted in the Venereal Disease Division¹ it was shown that most of the differences between areas in the final accomplishments of contact investigation could be explained by differences in the number of contacts obtained per patient. This factor indicates the importance of good interviewing.

Another study was recently completed on the number of contacts named by 2,000 individual patients with primary and secondary syphilis who gave some contact information.¹ Amazing variation was revealed in the number of contacts named by different individuals. Every patient named at least one contact, and the majority of the patients named two or three contacts. Moreover, 23 per cent of the patients named five or more contacts and 4 per cent named eight or more. It is extremely important that interviewers should be aware that certain patients will name many contacts

and that a minority of patients will name only one contact.

A good interview is the first step in successful contact investigation. Contacts must then be located, examined and placed under treatment if necessary. In general, areas reporting high contact ratios do as well in locating and examining as do areas with low contact ratios. In other words, high contact ratios have not been accomplished by a lowered quality of identifying information or by the addition of persons with little likelihood of being infected. As in interviewing, tact, diplomacy and speed are essential to successful investigation. Speed is doubly important in locating infections before they can be transmitted and in the location of migratory persons. The goal in one area is to have each contact located and examined within four days after being named by the patient.² Proper precautions must of course be taken to re-examine contacts with no obvious signs or symptoms at the first examination, particularly those recent contacts who may be suspected of being in the incubation period of syphilis.

The objective of contact investigation is to prevent the spread of infection, and it is therefore of paramount importance to locate, examine and treat contacts while they are in the open lesion stage. For the period from July to December, 1947 the average number of contacts with primary and secondary syphilis brought to treatment through contact investigation of open lesion syphilis varied from a low of .06 in one state to .29 in another. In certain areas this index has been as high as .47. Because many patients pass into the latent stage before location and examination are accomplished and because lesions are often fleeting or almost non-existent, this lesion to lesion ratio of .47 appears to be a very creditable performance and one which we believe could be attained in any area which intensifies its efforts to do efficient contact investigation.

Perhaps the data from a special experi-

ment in Arkansas² will illustrate what can be done:

Primary and secondary patients	
diagnosed.....	201
Contact index*.....	3.26
Epidemiologic index†.....	1.61
Brought to treatment index‡....	0.83
Lesion to lesion index§.....	0.47

It should be noted that each contact brought to treatment with primary or secondary syphilis is in turn included in the enumeration of cases diagnosed and thus presents the opportunity for further contact investigation. There is no duplication of count in the brought to treatment index or lesion to lesion index.³

Contact investigation on syphilis patients treated in public clinics and hospitals does not reach into all chains of infection. The private physician plays a vital rôle in syphilis control as he does in the control of other communicable diseases. Without his cooperation and active interest, the epidemiologic attack on syphilis cannot strike with full force. His friendly, confidential relationship with his patient offers advantages in obtaining information which the physician needs to protect his patient from reinfection and to contribute to the general public health. But physicians are busy men, and often they would welcome competent help in locating the contacts of their patients. This is especially true when contacts have moved to or live in other communities, when identification is difficult or when an infected contact refuses treatment for some reason. The health department can be helpful in many ways, and a close working relationship between the

* Contact index is the ratio of the number of contacts reported to the total number of previously untreated cases in the diagnostic category.

† Epidemiologic index is the ratio of the number of infected persons identified through contact investigation to the total number of patients diagnosed.

‡ Brought to treatment index is the ratio of the number of previously unknown cases found through contact investigation to the total number of patients diagnosed.

§ Lesion to lesion index is the ratio of the number of contacts with primary and secondary syphilis brought to treatment as a result of contact investigation to the number of cases of primary and secondary syphilis diagnosed.

physician and the health department is invaluable to both in their joint effort to control the spread of disease.

With the development of intensive schedules of therapy which lend themselves to out-patient treatment, more and more patients may be handled on an ambulatory basis by private physicians. Physicians have clearly demonstrated their growing interest in all phases of venereal disease control, and it is hoped that the joint efforts

of the physician and the health department in interviewing patients and examining contacts will continue.

REFERENCES

1. Office of Statistics, Venereal Disease Division, U. S. Public Health Service. Unpublished data.
2. EASLEY, E. J., PARKHURST, G. E. and SWANK, R. R. The 100-day experiment in contact investigation in Arkansas. *Ven. Dis. Inform.*, 29: 13-19, 1948.
3. ISKRANT, A. P. and KAHN, H. A. Statistical indices used in the evaluation of syphilis contact investigation. *Ven. Dis. Inform.*, 29: 1-6, 1948.

Transmission of Disease by Transfusion of Blood and Plasma*

JAMES R. CANTRELL, M.D. and MARK M. RAVITCH, M.D.

Baltimore, Maryland

RECENT years have brought a dramatic increase in the use of whole blood and blood plasma. As the establishment of blood banks made blood and plasma readily available, it became practicable for the first time to give transfusions

enormous increase in the use of blood and plasma. This is exemplified in Figure 1 which shows the growth of transfusion therapy at the Johns Hopkins Hospital from 1939 to 1946. In the first year after the organization of the blood bank 1,000

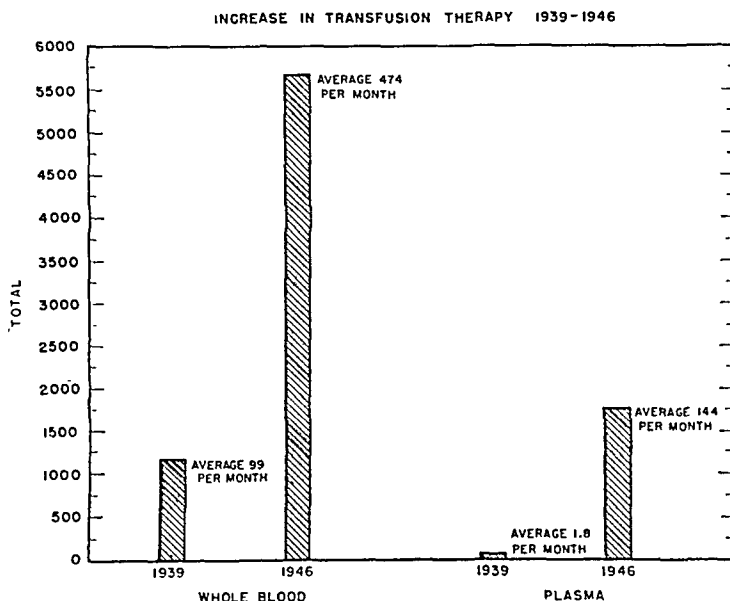


FIG. 1. Transfusion therapy at the Johns Hopkins Hospital in the first year of operation of the blood bank and in 1946.

to large numbers of patients who formerly had barely survived without transfusion, and it was found that five or six or even ten transfusions might save a life while the one or two considered adequate in the past had failed. The extension of the indications for transfusion and the advancement of surgery to permit successful performance of operations of a magnitude previously rarely attempted have combined to produce an

blood transfusions and 22 plasma transfusions were given; in 1946 there were 5,500 blood transfusions and 1,800 plasma transfusions. At present almost every large hospital has a formally organized blood bank of its own and those which do not are beginning to draw upon the recently developed centralized blood banks.

This widespread use of blood is not an unmixed blessing. Blood is a potent thera-

* From the Department of Surgery of the Johns Hopkins University School of Medicine and the Johns Hopkins Hospital, Baltimore, Md. Presented in part in the Forum on Fundamental Surgical Problems, Clinical Congress, American College of Surgeons, New York, September 10, 1947.

peutic agent and a dangerous one. The greatest danger inherent in the blood bank is the relative ease of making clerical errors which may result in the transfusion of incompatible blood. Rigorous application of a careful system of checks will minimize the frequency of such occurrences. A second danger inherent in transfusion therapy under any circumstance is the possibility of transmitting disease. It is obvious that this possibility increases in direct proportion to the increase in frequency of transfusion. It is our purpose to review the pertinent information available concerning the transmission of disease by blood and plasma transfusion, to determine practicable means for the elimination of this hazard and to present available methods which will allow the use of blood drawn from actually or potentially infected donors without risk of infection should transfusion with such blood be necessary or practical.

DISEASES CAPABLE OF TRANSMISSION BY BLOOD TRANSFUSION

The diseases most commonly known to be transmitted by transfusion are syphilis and malaria but during recent years homologous serum hepatitis has become of equal if not greater importance. It is routine practice in transfusion centers to employ precautionary measures to attempt to eliminate the transmission of syphilis and malaria and, to a lesser extent, of transfusion hepatitis. Precautions are required by law in some states. In Massachusetts, for example, the laws governing transfusion therapy read “. . . No person shall introduce the blood or any unsterilized fraction of the blood or tissue of any donor into the body of any recipient unless said donor has never had syphilis or malaria and is free from any dangerous disease, so far as such freedom from past and present infection can be determined by . . . a carefully taken history as to past or present infection with syphilis or malaria . . . and a careful physical examination.”¹

With the exception of syphilis and malaria, the diseases which have been re-

ported to be transmitted by blood transfusion are few. Baugess² reports two cases and Harrell³ a single case of measles transmitted to infants, the donors being in the incubation period at the time of bleeding. Robertson⁴ and J. R. Blalock⁵ each report a case of smallpox transmitted by transfusion. Three cases of transfusion typhus^{6,7,8} have been reported from Europe. Levick⁹ reports from England a single case of influenza transmitted by transfusion. Hendrick¹⁰ in her review of the subject cites three cases of tuberculosis reported from Europe by Opitz in 1925. Relapsing fever, due to the *Spirillum recurrentis* of Obermeier, developed following transfusion in six patients reported by Wang and Lee.¹¹ Beckman¹² reports a case of fatal encephalitis following transfusion of blood taken from a donor in whom chickenpox developed three days after bleeding. A single case has been reported¹³ of gonorrheal arthritis appearing in an eight months old male infant after two transfusions from his gonorrheal mother. A case of *B. Suipestifer* septicemia has been observed in the Venereal Disease Clinic of the Johns Hopkins Hospital following transfer of therapeutic malaria.¹⁴ The possibility of transmitting the above diseases is slight and it is believed that a reasonably complete and accurate history and an adequate physical examination should disclose donors suffering from these diseases or still in the infective prodromal stage.

HOMOLOGOUS SERUM HEPATITIS

Although jaundice following the injection of human tissue extracts was recognized and reported as early as 1885 by Lürman,¹⁵ it is only within recent years that homologous serum hepatitis has attracted widespread attention. Findlay and MacCallum¹⁶ in 1937 reported its occurrence after vaccination against yellow fever, and McNalty¹⁷ in 1938 discussed its appearance following the use of pooled measles convalescent serum. With the outbreak of the recent war when large numbers of troops were vaccinated against yellow fever, homologous serum hepatitis became recognized as a matter of

universal concern. Between January 1, 1942, and July 1, 1942, over 28,000 cases of hepatitis resulting in sixty-two deaths had occurred subsequent to yellow fever vaccination of about 2½ million persons.¹⁸ Subsequent investigations showed that the icterogenic agent was contained in the human serum which had been used as a vehicle and stabilizer for the immunizing agent.^{19,20} Since that time similar cases of hepatitis and jaundice have been recognized following the administration of whole blood and more particularly of plasma. Reports from civilian hospitals are few but significant.^{21,22} Six cases of jaundice following transfusion therapy and twice this number following therapeutic malaria transfer, all presumably cases of homologous serum hepatitis, have been observed at the Johns Hopkins Hospital. Recent reports of military experiences have indicated that in battle casualties this disease was a rather frequent occurrence attendant upon the use of large quantities of pooled plasma.²³ The disease is a serious one and its development following transfusion therapy must be regarded as a grave complication.

The exact incidence of homologous serum hepatitis following transfusion therapy is not known. Spurling, Shone and Vaughn in England²² found an incidence of 7.3 per cent among 1,054 recipients followed five months or longer after receiving pooled plasma or serum. They were able to discover only six doubtful cases of homologous serum hepatitis in 891 recipients of whole blood transfusions taken from single donors. Grossman and Saward²¹ report an incidence of 1.6 per cent in recipients of 501 transfusions of commercial pooled plasma. The incidence among war casualties who received transfusion therapy was about 2 to 3 per cent²⁴ and this figure seems to represent a fair average. Such an incidence assumes an even more disturbing significance when it is realized that this disease carries with it a fatality rate of 2 to 3 per cent.²⁴ This is ten times higher than that of infectious hepatitis which it so closely resembles.

The exact relationship of homologous serum hepatitis and infectious hepatitis has not been determined. The etiologic agents do not seem to be identical, certain significant differences having been definitely established. The properties of the etiologic agent of each of these diseases suggest that they are viruses. Neither agent, however, has been visualized by the electron microscope^{25,26} nor have attempts to cultivate them on ordinary or chick embryo media been successful.²⁰ No specific serologic test has as yet been found.^{20,27,28} The most important hindrance to the study of these diseases has been the lack of any susceptible laboratory animal.^{20,29,30,31,32} Transmission experiments have, therefore, been limited to human volunteers.

There are certain similarities between the causative agents of the two diseases. Both pass through bacteria-trapping filters.³¹⁻³⁴ Both survive heating at 56°C. for thirty minutes.³⁰ Both survive freezing for a period of years³⁵ and no diminution of virulence has been noted after storage at 4°C. for periods up to one year.³² Storage at room temperature for one year does not seem to destroy the viruses.³⁶ Both survive exposure to the ordinary bactericidal agents for long periods of time.^{34,37} The disease processes are clinically similar though not identical and the pathologic lesions are indistinguishable.³⁸

A distinction between the two diseases was suggested by the rather constant difference in the incubation periods, infectious hepatitis usually appearing in less than forty days after exposure, while homologous serum hepatitis becomes manifest from fifty-five to one hundred thirty-five days after transfusion. The onset of infectious hepatitis is often accompanied by high fever whereas homologous serum jaundice produces relatively little fever.³⁵ Differences in the method of transmission are significant. The virus of infectious hepatitis may be recovered from the feces of infected patients and the disease is readily produced by oronasal inoculation with material from this source.^{31,33,35,41,42,43,48} Epidemiologic observations lend strong support to the theory

of alimentary transmission. Transmission of infectious hepatitis by the parenteral injection of blood products has only occasionally been successful and does not seem to be the natural method of infection.^{30, 39, 40, 44, 45} The virus of homologous serum hepatitis, however, routinely produces a typical infection when injected parenterally, and attempts to produce the disease by oral inoculation with blood or blood products have been almost uniformly unsuccessful.^{35, 41, 43} This agent has not been recovered from the feces of an infected patient.^{35, 45, 46} The transmission of this disease is apparently accomplished solely by artificial means, that is, by parenteral injection of blood or blood products. Recent evidence indicates that the disease may be transmitted by contaminated syringes or needles.^{47, 49, 50, 51} Each of these diseases produces a definite long-lasting homologous immunity.^{32, 35, 42, 44, 52, 53} No cross immunity has been demonstrated^{35, 44, 53} suggesting at least a definite antigenic difference between the two viruses. From the fact that many persons over thirty years of age show a definite resistance to the virus of infectious hepatitis,^{42, 54} it has been inferred that many subclinical infections occur with resultant complete or partial immunity. This may be true for homologous serum hepatitis since it is known that some recipients of icterogenic material do not develop clinically recognizable hepatitis. The fatality rate of the two diseases is strikingly different, that of homologous serum hepatitis being ten times as great as that of infectious hepatitis.²⁴ In view of these dissimilarities it would seem most likely that the etiologic agents of these diseases are similar but not identical.

In any case, there can be little doubt that the increased incidence of serum hepatitis among the armed forces and civilians is due to the increased use of pooled plasma. The amount of icterogenic plasma required to contaminate a pool is extremely small, as little as 0.01 cc. being sufficient to transmit the disease.³¹ If but one donor of a 5,000 unit pool were infected, each plasma unit from this pool would still contain five times

the amount of icterogenic plasma necessary to transmit the disease.

PREVENTION OF HOMOLOGOUS SERUM HEPATITIS

Our present methods for preventing homologous serum hepatitis are grossly inadequate. The following, however, are worthy of consideration:

The Control of Donors. Although it has never been proven that carriers of homologous serum hepatitis exist, most blood banks exclude donors with a history of jaundice. While this measure is probably justified because of the possibility that a carrier state exists, it is somewhat illogical since donors in the presymptomatic stage of the disease are presumably the source of greatest danger. The icterogenic agent has been demonstrated in the blood stream of an experimentally inoculated human volunteer as long as eighty-seven days prior to the onset of clinical hepatitis and is present in the blood until the onset of clinical symptoms.^{36, 41} Although there is not as yet sufficient evidence available to justify definite conclusions, it seems that the virus probably disappears from the blood soon after the onset of jaundice. Data concerning the presence of the virus in the blood following recovery from the disease are not available. We cannot expect to reduce significantly the number of cases of homologous serum hepatitis by elimination of donors.

Reduction in the Size of Pools. Since a single unit of icterogenic plasma will contaminate a very large pool, it would seem logical to eliminate the pooling system and to use only individual units of plasma made from the blood of a single donor. Such a plan would reduce the number of people exposed to the infected blood. On the other hand, there is some danger of incompatibility reactions in the use of unpooled plasma, and such a policy would reduce the production of plasma to a much less efficient process and thereby decrease the ready availability of plasma created by the use of large scale production methods. A compromise method would be the use of smaller

plasma pools using blood drawn from six to eight donors, thereby reducing the number of recipients exposed.

The Use of Plasma Fractions. When the subject of homologous serum hepatitis was first brought into prominence it was noted that no cases were observed following the administration of gamma globulin.³⁵ This suggested that perhaps this fraction of the plasma might contain some substance protective against the icterogenic agent. Data on this aspect of the problem are inconclusive^{23, 55, 56, 57, 58} but the method seems to offer little promise for preventing transfusion hepatitis. Similarly we have found no reported cases of transfusion hepatitis following the use of human serum albumin. This would suggest that the agent is destroyed in the process of fractionation.

Ultraviolet Irradiation. The studies of Oliphant³² suggest that the virus of homologous serum hepatitis may be inactivated by exposure to ultraviolet irradiation. Evidence for this is not conclusive. Final application of this method must await further studies of the effect on the virus. The recent studies of Wolf⁵⁹ and his co-workers indicate that plasma irradiated by the method of Oppenheimer and Levinson⁶⁰ is not altered chemically and may be given to human beings without ill effect. The technical difficulties of irradiating plasma in large quantities constitute a considerable obstacle which has not as yet been overcome.

Fifth, it may be possible to heat plasma to a temperature lethal to the virus without rendering the plasma unfit for parenteral use. Lastly, the capacitron⁶¹ offers another avenue of investigation.

TRANSFUSION SYPHILIS

The first recorded case of transfusion syphilis was reported by Fordyce in 1915⁶² and we have been able to collect almost 100 cases cited in the literature since that time. Since this number probably represents but a small fraction of the number of cases which have gone unrecognized or unreported, the importance of this complication of transfusion therapy cannot be

ignored. Twelve cases of transfusion syphilis are known to have occurred in the Johns Hopkins Hospital.⁶³ None of these, however, has occurred since the organization of the blood bank in 1939.

Syphilis is primarily of interest in blood bank administration from the point of view

TABLE I
INCIDENCE OF POSITIVE SEROLOGIC TESTS FOR SYPHILIS IN
BLOOD DONORS AT THE JOHNS HOPKINS HOSPITAL
BLOOD BANK—1946

	Total Donors	S.T.S. Positive Donors	Per cent
White.....	4212	50	1.2
Colored.....	3295	437	13.3
Total.....	7507	487	6.5

of the patient's welfare and the prevention of transmission of the disease to recipients by way of transfusion. Of great practical interest to the blood bank, however, is the fact that large quantities of blood must be discarded because of positive serologic tests for syphilis. Table I shows the incidence of positive serologic tests for syphilis among donors bled in the blood bank of the Johns Hopkins Hospital during 1946. It must also be remembered that all donors with a history of syphilis or of antisypilitic therapy were rejected and therefore are not included in these figures. MacNamara⁶⁴ has shown that syphilis is not transmitted by transfusion of blood drawn from donors with tertiary syphilis. There is also reason to believe that blood drawn from syphilitic patients other than those in the late stages can be used without infection. If such blood could in some manner be made available for use a very considerable waste would be prevented.

Transfusion syphilis differs from the disease as contracted by genital or extra-genital inoculation only in the absence of the chancre. The first manifestation of the disease is almost invariably the development of secondary lesions although in a few patients this phase has been absent or so insignificant as to escape notice and the

late manifestations have been the presenting symptoms. Klauder and Butterworth⁶⁵ in 1937 analyzed thirty reported cases of transfusion syphilis and found that the incubation period varied from four to sixteen weeks, the majority of the patients showing secondary lesions between the eighth and the tenth weeks. This observation corresponds exactly to the incubation period of the disease as contracted by the usual genital or extragenital invasion, the chancre appearing in about three weeks and the secondary lesions developing about six weeks after the appearance of the chancre. As far as is known, there is no difference in the prognosis of transfusion and of natural syphilis and there is no recognized difference in the response to therapy.

METHODS FOR THE PREVENTION OF TRANSFUSION SYPHILIS

Prior to the organization of blood banks it often happened that no test for syphilis in the donor was performed before transfusion. This was due either to lack of technical facilities or to the emergency nature of the transfusion. Such was the case in 75 per cent of the forty-one cases of transfusion syphilis collected by Eichenlaub and Stolar⁶⁶ in 1939. Since the establishment of blood banks we no longer face these problems. With a large store on hand at all times blood is routinely kept long enough to allow serologic tests for syphilis to be performed before the blood is used. In the cases collected by Eichenlaub and Stolar⁶⁶ 39 per cent of the donors had, or presumably would have had, a negative serologic test for syphilis immediately before giving blood since they were in the incubation period of the disease before the appearance of the chancre. In addition, as seen in Table II,⁶⁷ in every stage of syphilis a certain fraction of the patients will have negative serologic tests and except in secondary syphilis the fraction is substantial. In the group of infective though seronegative donors lies the hazard of transfusion syphilis. It seems obvious that despite faithful performance

of the most accurate serologic tests available we may still encounter cases of transfusion syphilis. What further measures are available to us to prevent such an accident?

Mütermilch⁶⁸ in 1932 attempted to prevent infection by adding cyanide of mercury

TABLE II
INCIDENCE OF NEGATIVE SEROLOGIC TESTS IN UNTREATED
SYPHILITICS

Type	Seronegative Per cent
Primary.....	30
Secondary.....	0.9
Latent.....	0 (serol. diag.)
Late (except neurological).....	18.8
Diffuse meningo-vascular.....	10.1
Paresis.....	11.3
Tabes.....	18.1

to infected blood in a concentration of 1 mg. per ml. The toxicity of this drug and the large amounts required render this method unsafe. Furthermore, Gougerot and his co-workers⁶⁹ report two cases and Hudelo⁷⁰ a third case of transfusion syphilis which developed in spite of the addition of 5 mg. of cyanide of mercury to 10 ml. of serum which was injected intravenously. This method cannot be considered practical or safe.

Kast, Peterson and Kolmer⁷¹ in 1939 advocated the addition of neoarsphenamine to whole citrated blood to prevent transfusion syphilis, reporting their well controlled *in vitro* and rabbit inoculation experiments which demonstrated the high treponemocidal effects of arsphenamine and neoarsphenamine. They found both drugs completely treponemocidal in a dilution of 1:10,000. If such a concentration were used with the usual 500 ml. transfusion, the recipient would receive 50 mg. of the drug or approximately one-fifteenth of the average single therapeutic dose. In the concentration recommended, 1:10,000, the drug is not hemolytic and does not agglutinate the red cells.⁷¹ Kast et al. also reported the administration of transfusions containing this concentration of neoarsphenamine or arsphenamine to eight persons with no evidence of toxicity. Occasionally the use of such blood might be contraindicated and in any case one would have to accept

the risk of a small but definite incidence of arsenical sensitivity reactions.

In 1941 Turner and Discker⁷² and Bloch⁷³ independently demonstrated that whole blood inoculated with active treponemes loses its infectivity before ninety-six hours of storage at 4°C., and in 1942 Ravitch and Chambers⁷⁴ showed that plasma inoculated with active treponemes and then frozen lost its infectivity after less than forty-eight hours in the frozen state. This experimental work suggests a practical method of preventing transfusion syphilis. Routine storage of all blood in the refrigerator at 4°C. for four days would prevent any recipient from acquiring syphilis even if serologic tests were not made. Similarly, known syphilitic blood may be used for the preparation of plasma with no danger of transmitting syphilis since plasma is routinely kept frozen at least a week before use while cultures are being made. Prior to the organization of the blood bank twelve cases of transfusion syphilis were observed in the Johns Hopkins Hospital. Since 1939, however, with over 40,000 blood and plasma transfusions, no cases have been recognized. Considering the figures for the incidence of infectious seronegative donors (Table II) it must be concluded that simple storage at 4°C. must have prevented a considerable number of cases of transfusion syphilis. No attempt has been made to require four-day storage of all blood and in view of the absence of cases of transfusion syphilis such a policy would not seem to be indicated. If, however, in a given center the proportion of seropositive donors were greater or the incidence of transfusion syphilis appreciable or if, for some reason, one desired to use seropositive blood, adoption of such a plan would be advisable. Addition of one of the arsenicals provides a possible means of attack on the problem.

The use of seropositive blood for the production of plasma offers a method for eliminating the waste incurred in rejecting donors with a history of syphilis or anti-syphilitic therapy and that incurred in discarding all seropositive blood. Trans-

fusion with such plasma will temporarily render positive the recipient's serologic test for syphilis. This problem is under study by one of us (M. M. R. with T. Farmer and B. Davis)⁸⁷ and results indicate that the serologic tests for syphilis revert to negative within one to two weeks.

TRANSFUSION MALARIA

The possibility of transmitting malaria by transfusion has long been known. The first case of accidental transmission recorded is that of Woolsey⁷⁵ who in 1911 reported the development of malaria in a recipient after a direct artery-to-vein transfusion. Since that time there have been sixty reports of transfusion malaria occurring in non-endemic areas, twenty of these having been reported during the past eight years. Malaria is endemic in only a very small section of the United States. This area has constantly shrunk and the small group of persons in this country harboring active or latent malarial infections has gradually diminished. Since World War II, however, the situation has changed. With the return to the United States of the large numbers of servicemen who served in malarial zones, the number of malarial infections, both latent and active, in all parts of the United States has increased greatly. The geographic and epidemiologic factors are such that an increase in mosquito-borne malaria is not expected in most regions of the United States. However, the increase in malaria in our population and the concomitant increase in transfusion therapy will almost surely bring an increase in transfusion malaria unless preventive measures are taken. Thus, malaria now presents a considerable hazard in transfusion therapy and has become a point of vital interest to our rapidly increasing and expanding blood banks.

Malaria inoculata does not differ significantly in its characteristics from naturally incurred malaria. It has been noted⁷⁶ that in quartan malaria the incubation period, dated from the onset of fever, is eight days or less when the disease is contracted

artificially (trophozoite) but is about thirteen and a half days when acquired naturally (sporozoite). The duration of the initial attack, however, is not significantly different, the characteristics of the attacks and the paroxysms are the same and the recurrence rate is approximately the same. Except for the length of the incubation period these observations hold equally for the other types of malaria.

PREVENTION OF TRANSFUSION MALARIA

The most obvious and most frequently advocated method for the prevention of transfusion malaria is the rigid questioning of donors concerning a past history of clinical malaria or their past residence in an area in which malaria is endemic, and the rejection of all donors who give a positive history of either. The task of obtaining an accurate and reliable history may be extremely difficult. In this connection we must appreciate the remarkably long periods of latency which are compatible with a still active and virulent malarial infection capable of being transmitted by blood transfusion. Jankleson⁷⁷ reports a case of transfusion malaria in which the donor's last possible exposure to infection had occurred forty years before and there are several instances reported with a latent period of twenty-five years. Reliance upon history to rule out malarial donors will lower the incidence of transfusion malaria but will not prevent it. In addition, this plan has the obvious disadvantage of reducing the number of donors available for bleeding. If we adopt the safer policy of rejecting all donors who have at any time lived in a malarial area the number of acceptable donors becomes even more limited, especially in view of the large number of young men recently returned from service in endemic zones. In the regions of the United States in which malaria is endemic such a policy would be almost prohibitive. Examination of the known facts concerning the transmission of malaria would suggest that a policy of wholesale rejection of donors is not necessary.

Ackerman and Filatov⁷⁸ reported the most thorough investigation of this problem in 1934 when they studied the survival of tertian plasmodia in blood stored for varying lengths of time under conditions simulating those now found in blood banks. Survival was tested by smear and by inoculation of patients suffering from "... central nervous system diseases in which malarial therapy was indicated." Their experiments showed that tertian plasmodia did not survive after ninety-six hours of storage. Clinical experience supports this conclusion. In none of the reported cases of tertian transfusion malaria had the blood been stored as long as four days. The same conclusions do not seem to stand without reservation for the other forms of malaria. Two cases of quartan malaria following transfusion with five-day old bank blood are reported by McClure and Lam⁷⁹ and a third case of transfusion quartan malaria following transfusion with blood stored for eight days is cited by Antschelewitsch.⁸⁰ There are two cases of transfusion malaria recorded in the histories of the Johns Hopkins Hospital. The first was included in a report by F. Howell Wright in 1938⁸¹ and occurred in a nine-month infant who received a transfusion of fresh citrated blood from his father who had had clinical malaria twelve years previously but had been asymptomatic since. The parasites in the baby's blood were demonstrated to be quartan. No parasites could be demonstrated in the blood of the father. The second case occurred in 1946 in a sixteen year old boy with congenital hemolytic jaundice who was brought into the hospital for splenectomy. On the day of operation he received two transfusions of 500 cc. of whole citrated blood. Recovery was uneventful and he was discharged from the hospital. He was re-admitted six weeks later with a history of sudden onset of severe chills and high fever beginning four weeks after discharge and six weeks after his two blood transfusions. He had been having chills regularly every seventy-two hours during the two weeks prior to ad-

mission. Quartan parasites were readily demonstrated in his blood and his paroxysms disappeared immediately upon the institution of atabrine therapy.

The donors of the transfusions which the patient had received were examined but neither could be proved to have a malarial infection. The first donor was a forty-three year old white male of Sicilian birth who migrated to this country at the age of seven years. He gave no history of malaria. The second donor was a twenty-two year old white male who had been discharged from the Army a short time prior to donating blood, having served in Africa and the South Pacific and having had a febrile illness in the latter area which was not proved to be malaria. Neither donor had a palpable spleen and smears taken after subcutaneous injection of adrenalin were negative for parasites. The patient was born in New York, moved to Maryland at the age of one and one-half years and had never been exposed to malaria. He gave no history of any previous illness suggesting malaria. In view of these facts it is believed that despite the failure to demonstrate parasites in the blood of the donors it may be assumed that this represents a case of transfusion malaria. As these transfusions were given after the blood had been stored for periods of forty-eight and ninety-six hours, respectively, they throw no new light on the length of survival of quartan plasmodia when stored under blood bank conditions. Until further experimental work is done with quartan and malignant tertian parasites it would seem inadvisable to depend on storage alone to prevent malaria inoculation.

The second obvious method of rendering blood non-infectious which is actually or potentially infected is the introduction of a plasmodicide into the blood. Such attempts have thus far been unsuccessful. Quinine in concentrations up to 1:1,000 has no effect⁷⁸ nor have any of the other antimalarial drugs proved more effective.⁸²

Benign tertian or quartan malaria inoculata has long been recognized to be a rela-

tively mild form of malaria, particularly sensitive to antimalarial therapy. Thoroughman⁸³ in Soochow, China, attempted to solve the problem from this point of attack. In that highly endemic area 176 transfusions from unselected donors produced transfusion malaria in 53 per cent of the recipients. In his experiments he considered all donors to be potentially infected and accordingly, in a series of thirty-four transfusions, gave all recipients 0.9 Gm. of quinine per day for the three days following transfusion. No infections occurred although normally fifteen persons would have been expected to develop clinical malaria. A similar plan was proposed by R. R. Officer⁸⁴ of Australia who inoculated five subjects with blood drawn from donors with proved benign tertian malaria. He protected the recipients by simultaneously beginning a course of quinine-atabrine-plasmochin therapy and again no infections were observed. These antimalarial drugs may probably be advantageously supplanted by the newer drugs, chloroquine and chlorguanide. Obviously such methods are not meant for general use in non-endemic areas. They do, however, present a feasible method for the prevention of transfusion malaria in instances in which transfusion with potentially infected blood is a necessity regardless of the risk of infection. Such a situation might arise in military medical practice or in civilian practice in areas of high endemicity. In tropical regions and to a lesser extent in endemic areas of the United States such a program might be advantageous.

As yet no method is known which will allow the safe use of fresh whole blood drawn from donors with actual or potential malarial infection. However, it is not necessary to refuse all donors who give a history of malaria or of residence in an endemic area. The plan now in use in the blood bank at the Johns Hopkins Hospital is supported by the work of Lozner and Newhouser⁸⁵ who showed that plasma prepared from blood proved to be infected with active quartan or falciparum parasites could be given safely without risk of infection. They

prepared plasma from infected blood and stored it at -20°C . for periods varying from five to thirty-four days. In twenty transfusions using this plasma no cases of malaria inoculated were observed. Since plasma is necessarily kept for at least seven days while cultures are being made, the safety factor is more than adequate. It is significant that although storage at -20°C . kills the plasmodia, freezing at -72°C . is used as the method of preservation of plasmodia, the parasites retaining their virulence for long periods of time at this temperature.⁸⁶ The same is, of course, true of *Treponema pallidum*. An additional factor of safety lies in the obvious fact that the parasites, which are for the most part within the red cells, are almost entirely removed in the preparation of plasma.

It would seem then that at the present time there is no method which can be adopted by blood banks which will safely permit the use of whole blood potentially or actually infected with malaria except the concomitant use of antimalarial therapy for the recipient. It is no longer necessary, however, to reject donors giving a positive history of malaria or of exposure to malaria. Frozen plasma prepared from the blood of suspected donors can be used with safety.

SUMMARY

1. The possibility of transmission of disease through transfusion has increased in proportion to the increase in transfusion therapy. The diseases which must be considered most seriously are homologous serum hepatitis, syphilis and malaria.

2. The incidence of homologous serum hepatitis has been greatly increased by the use of pooled plasma. Reducing the size of plasma pools will limit the incidence of the disease. Fractionation of plasma is one avenue of approach to the problem. Physical methods may inactivate the virus without injuring the plasma.

3. In spite of careful selection of donors a low but definite incidence of transfusion syphilis may be expected. Blood containing active treponemes may be rendered safe

for use either by adding an arsenical in a dilute concentration or by storage at 4°C . for ninety-six hours. Infected blood may also be utilized by converting it to plasma and storing it at -20°C . for forty-eight hours. Recipients of such plasma will develop positive serologic tests for syphilis for from one to two weeks. Such a program would prevent the waste of large quantities of blood now discarded because of positive serologic tests for syphilis.

4. No method has been found which will allow blood banks to utilize safely whole blood infected with malaria. If under some circumstances it should be necessary to employ actually or potentially infected blood, transmission can be prevented by the concurrent institution of antimalarial therapy. Plasma made from infected blood and stored at -20°C . for five days can be used without danger. Persons with a past history of malaria or of exposure to malaria may, therefore, be accepted as donors.

REFERENCES

1. Regulations relative to use of blood or other tissue for purposes of transfusion. Adopted by Massachusetts Dept. of Public Health, March 14, 1939. *New England J. Med.*, 220: 538, 1939.
2. BAUGESS, H. Measles transmitted by blood transfusion. *Am. J. Dis. Child.*, 27: 256, 1934.
3. HARRELL, H. P. Measles transmitted by blood transfusion. *J. A. M. A.*, 82: 1812, 1924.
4. ROBERTSON, B., BROWN, A. and SIMPSON, R. Blood transfusion in children. *Northwest. Med.*, 20: 233, 1921.
5. BLALOCK, J. R. Smallpox without eruption following blood stream inoculation; report of a case following blood transfusion. *Ann. Clin. Med.*, 4: 722, 1926.
6. DORMANNS, E. and EMMINGER, E. Transmission of typhus from man to man by transfusion during the incubation stage. *München. med. Wchnschr.*, 89: 599, 1942.
7. GEER, V. M. Transmission of typhus by means of transfusion. *Soviet Med.*, 6: 27, 1942.
8. GOLANDSKY. On the possibility of transmitting typhus exanthematicus through blood transfusion. *Voenno Med. J.*, 3: 1933 (quoted by Ackermann and Filatov, cf. 78).
9. LEVICK, C. B. An unusual complication of blood transfusion. *Brit. M. J.*, 2: 847, 1931.
10. HENDRICK, H. Diseases transmitted in blood transfusions. *Proc. Inst. Med. Chicago*, 10: 185, 1935.
11. WANG, C. W. and LEE, C. U. Malaria and relapsing fever following blood transfusion. *Chinese M. J.*, 50: 241, 1936.
12. BECKMAN, T. M. On transfer of infection through

- blood transfusion. *Acta chir. Scandinav.*, 76: 615, 1935.
13. JANGU, A., OPRISIN, C. and DOMINGOVICI, N. Gonorrhoeal arthritis secondary to blood transfusion. *Monatschr. f. Kinderh.*, quoted in *J. A. M. A.*, 114: 999, 1940.
 14. MOHR, C. F. Personal communication.
 15. LURMAN, Eine Icterus Epidemie. *Berlin klin. Wchnschr.*, 22: 20, 1885.
 16. FINDLAY, G. M. and MACCALLUM, F. O. Note on acute hepatitis and yellow fever immunization. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 31: 297, 1937.
 17. McNALTY. Acute infectious jaundice and administration of measles serum: annual report of the chief medical officer of the Ministry of Health for 1937. London. His Majesty's Stat. Off., 1938.
 18. Editorial. Jaundice following yellow fever vaccination. *J. A. M. A.*, 119: 1110, 1942.
 19. FINDLAY, G. M., MACCALLUM, F. O. and MURGATROYD, E. Observations bearing on the etiology of infective hepatitis. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 32: 575, 1939.
 20. SAWYER, W. A., MEYER, K. F., EATON, M. D., BAUER, J. H., PUTNAM, P. and SCHWENTKER, F. F. Jaundice in army personnel in the western region of the United States and its relation to vaccination against yellow fever. *Am. J. Hyg.*, 40: 35, 1944.
 21. GROSSMAN, C. M. and SAWARD, E. W. Homologous serum jaundice following the administration of commercial pooled plasma. *New England J. Med.*, 234: 181, 1946.
 22. SPURLING, N., SHONE, J. and VAUGHN, J. The incidence, incubation period, and symptomatology of homologous serum jaundice. *Brit. M. J.*, 2: 409, 1946.
 23. GROSSMAN, E. B., STEWART, S. G. and STOKES J., JR. Post-transfusion hepatitis in battle casualties. *J. A. M. A.*, 129: 991, 1945.
 24. JANEWAY C. A. Present status of homologous serum jaundice. *Bull. U. S. Army M. Dept.*, 5: 3, 1946.
 25. MATHIESON D. R. Cited by Oliphant. The Harvey Lectures, 1943-1944.
 26. CHAMBERS, L., HEMMETZ, F. and NEEFE, I. R. Unpublished data cited by Neeffe. *M. Clin. North America*, 1407, 1946.
 27. EATON, M. D., MURPHY, W. D. and HANFORD, V. L. Heterogenous antibodies in acute hepatitis. *J. Exper. Med.*, 79: 539, 1944.
 28. OLITZKI, L. and BERNKOPF, H. Precipitation in infective hepatitis. *J. Infect. Dis.*, 77: 60, 1945.
 29. CAMERON, J. D. S. Infective hepatitis. *Quart. J. Med.*, 12: 139, 1943.
 30. OLIPHANT, J. W., GILLIAM A. G. and LARSON C. L. Jaundice following administration of human serum. *Pub. Health Rep.* 58: 1233, 1943.
 31. OLIPHANT, J. W. and HOLLANDER, A. Homologous serum jaundice; experimental inactivation of etiologic agent in serum by ultraviolet irradiation. *Pub. Health Rep.*, 61: 598, 1946.
 32. OLIPHANT, J. W. Jaundice following administration of human serum. The Harvey Lectures, 1943-1944. *Bull. New York Acad. Med.*, 20: 429, 1944.
 33. NEEFE, J. R. and STOKES, J., JR. Epidemic of infectious hepatitis apparently due to a water-borne agent. *J. A. M. A.*, 128: 1063, 1945.
 34. BEESON, P. B., CHESNEY, G. and MCFARLAN, A. M. Hepatitis following infection of mumps convalescent plasma. *Lancet*, 1: 814, 1944.
 35. NEEFE, J. R., GELLIS, S. S. and STOKES, J., JR. Homologous serum hepatitis and infectious hepatitis. *Am. J. Med.*, 1: 3, 1946.
 36. NEEFE, J. R., STOKES, J., JR., REINHOLD, J. G. and LUKENS, F. D. W. Hepatitis due to the injection of homologous blood products in human volunteers. *J. Clin. Investigation*, 23: 836, 1944.
 37. Memorandum of the Ministry of Health. *Lancet*, 1: 83, 1943.
 38. MAILLORY, T. B. Pathology of epidemic hepatitis and homologous serum jaundice. *New England J. Med.*, 236: 441, 1947.
 39. FRANCIS, T., JR., FRISCH, A. W. and QUILLIGAN, J. J. Demonstration of infectious hepatitis virus in presymptomatic period after transfer by transfusion. *Proc. Soc. Exper. Biol. & Med.*, 61: 276, 1946.
 40. HAVEN, W. P., JR. Unpublished experiments quoted by Paul, J. R., and coworkers. *J. A. M. A.*, 128: 911, 1945.
 41. PAUL, J. R., HAVEN, W. P., JR., SABIN, A. B. and PHILIP, C. B. Transmission experiments in serum jaundice and infectious hepatitis. *J. A. M. A.*, 128: 911, 1945.
 42. GAULD, R. Epidemiological field studies of infectious hepatitis in the Mediterranean theater of operations. *Am. J. Hyg.*, 43: 248, 1946.
 43. WITTS, L. J. Some problems of infective hepatitis. *Brit. M. J.*, 1: 739, 1944.
 44. NEEFE, J. R., STOKES, J., JR. and GELLIS, S. S. Homologous serum hepatitis and infectious hepatitis. *Am. J. M. Sc.*, 210: 561, 1945.
 45. NEEFE, J. R., STOKES, J., JR. and REINHOLD, J. G. Oral administration to volunteers of feces from patients with homologous serum hepatitis and infectious hepatitis. *Am. J. M. Sc.*, 210: 29, 1945.
 46. MACCALLUM, F. O. Transmission of arsenotherapy jaundice by blood. *Lancet*, 1: 342, 1945.
 47. SEEHAN, H. L. Epidemiology of infective hepatitis. *Lancet*, 2: 8, 1944.
 48. FOX, J. P., MANSO, C., PENNA, H. A. and MADUREIRA, PARA. Observations of the occurrence of icterus in Brazil following vaccination against yellow fever. *Am. J. Hyg.*, 36: 68, 1942.
 49. SALAMAN, M. H., KING, A. J., WILLIAMS, D. I. and NICOL, C. S. Prevention of jaundice resulting from antisyphilitic treatment. *Lancet*, 2: 7, 1944.
 50. BIGGER, J. W. Jaundice in syphilitics under treatment. *Lancet*, 1: 457, 1943.
 51. Editorial. Syringe transmitted hepatitis. *J. A. M. A.*, 129: 278, 1945.
 52. FINDLAY, G. M., MARTIN, N. H. and MITCHELL, J. B. Hepatitis after yellow fever inoculation. *Lancet*, 2: 301, 1944.
 53. HAVENS, W. P., JR. Experiment in cross immunity between infectious hepatitis and homologous serum jaundice. *Proc. Soc. Exper. Biol. & Med.*, 59: 148, 1945.
 54. NEEFE, J. R. Recent advances in the knowledge of "virus hepatitis." *M. Clin. North America*, 30: 1407, 1946.
 55. STOKES, J., JR. and NEEFE, J. R. Prevention and attenuation of infectious hepatitis by gamma globulin. *J. A. M. A.*, 127: 144, 1945.

56. GELLIS, S. S., STOKES, J., JR. FORSTER H. W. JR. BROTHER G. M. and HALL W. M. Use of human immune serum globulin in infectious hepatitis in the Mediterranean theater of operations. *J. A. M. A.* 128: 1158 1945.
57. DUNCAN, G. G., CHRISTIAN H. STOKES J., JR. REXER, W. F., NICHOLSON, J. T. and EDGAR, A. An evaluation of immune serum globulin as a prophylactic agent against homologous serum hepatitis. *Am. J. M. Sc.*, 213: 53, 1947.
58. ROBINSON, R. W., HAMBLIN, W. M., FLEMING, R. S. and QUEEN, F. B. Failure of immune serum globulin to prevent or modify infectious hepatitis of the homologous serum type. *Bull. U. S. Army M. Dept.*, 5: 258, 1946.
59. WOLF, A. M., MASON, J., FITZPATRICK, W. J., SCHWARTZ, S. O. and LEVINSON, S. O. Ultraviolet irradiation of human plasma to control homologous serum jaundice. *J. A. M. A.*, 135: 476, 1947.
60. OPPENHEIMER, F. and LEVINSON, S. O. A new method for the production of potent inactivated vaccines with ultraviolet irradiation. Quoted by Wolf and co-workers.⁵⁹
61. BRASCH, A. and HUBER, W. Ultrashort application time of penetrating electrons. *Science*, 105: 112, 1947.
62. FORDYCE, J. H. Some problems in the pathology of syphilis. *Am. J. M. Sc.*, 149: 781, 1915.
63. MOORE, J. E. The Modern Treatment of Syphilis. Baltimore, 1941. Charles C. Thomas.
64. MACNAMARA, W. L. The non-infectivity of blood in tertiary syphilis. *Am. J. Syph.*, 9: 470, 1925.
65. KLAUDER, J. V. and BUTTERWORTH, T. Accidental transmission of syphilis by blood transfusion. *Am. J. Syph., Gonorr., & Ven. Dis.*, 21: 652, 1937.
66. EICHENLAUB, F. J. and STOLAR, R. Syphilis acquired from transfusion and its control. *Pennsylvania M. J.*, 42: 1437, 1939.
67. EAGLE, H. Unpublished data.
68. MÜTERMILCH, S. Ways of preventing contamination with syphilis during transfusion. *Bull. Soc. franc. de dermat. et syph.*, 39: 273, 1932.
69. GOUGEROT, FIESINGER, BRUNO and DALLY. Deux cas de syphilisation par transfusion pour rajeunissement. *Ann. d. mal vén.*, 26: 174, 1931.
70. HUDDLO. Quoted by Gougerot. *Ann. d. mal vén.*, 86: 174, 1931.
71. KAST, C. C., PETERSON, C. W. and KOLMER, J. A. The treponemicidal activity of arsphenamine and neoarsphenamine in vitro with special reference to citrated blood. *Am. J. Syph., Gonorr. & Ven. Dis.*, 23: 150, 1939.
72. TURNER, T. B. and DISEKER, T. H. Duration of infectivity of *Treponema pallidum* in citrated blood stored under conditions obtaining in blood banks. *Bull. Johns Hopkins Hosp.*, 68: 269, 1941.
73. BLOCH, O., JR., Loss of virulence of *Treponema pallidum* in citrated blood at 5°C. *Bull. Johns Hopkins Hosp.*, 68: 412, 1941.
74. RAVITCH, M. M. and CHAMBERS, J. W. Spirochaetal survival in frozen plasma. *Bull. Johns Hopkins Hosp.*, 71: 299, 1942.
75. WOOLSEY, G., Transfusion for pernicious anemia; two cases. *Ann. Surg.*, 53: 132, 1911.
76. BOYD, M. F. Observations on naturally and artificially induced quartan malaria. *Am. J. Trop. Med.*, 20: 749, 1940.
77. JANKLESON, I. R. Transmission of malaria through injection of whole blood. *J. A. M. A.*, 97: 177, 1931.
78. ACKERMANN, V. and FILATOV, A. On the possibility of preventing transmission of malaria by blood transfusion. *J. Trop. Med.*, 37: 49, 1934.
79. McCLURE, R. D. and LAM, C. R. Malaria from bank blood transfusions. *Surg. Gynec. & Obst.*, 80: 261, 1945.
80. ANTSCHELEWITSCH, W. D. Transfusion von konserviertem Malarikerblut. *Folia haemat.*, 57: 406-1937.
81. WRIGHT, F. H. Accidental transmission of malaria through the injection of whole blood. *J. Pediat.*, 12: 327, 1938.
82. MARSHALL, E. K. Unpublished data.
83. THOROUGHMAN, J. C. Malaria transmission by blood transfusion. *Chinese M. J.*, 58: 682, 1940.
84. OFFICER, R. R. Experimental transfusion with malaria infected blood. *M. J. Australia*, 1: 271, 1945.
85. LOZNER, E. L. and NEWHOUSER, L. R. Studies on the transmissibility of malaria by plasma transfusions. *Am. J. M. Sc.*, 206: 141, 1943.
86. COGGESHALL, L. T. Preservation of viable malaria parasites in the frozen state. *Proc. Soc. Exper. Biol. & Med.*, 42: 499, 1939.
87. RAVITCH, M., FARMER, T. and DAVIS, B. Use of blood donors with positive serologic tests for syphilis. *J. Clin. Investigation*, in press.

Seminars on Congestive Failure

Mechanisms of Salt and Water Retention in Heart Failure*

ARTHUR J. MERRILL, M.D.

Atlanta, Georgia

DURING the development of chronic congestive heart failure, salt and water are retained. The cause of this retention has been the subject of a lively recent controversy. The final answer is not yet clear but a more rational solution to certain phases of the problem has been discovered.

The concept of fluid being forced into the tissues by an increased venous pressure seems no longer tenable. Such a situation should result in hemoconcentration whereas chronic congestive heart failure is associated with hemodilution.^{1,2} Furthermore, any *sustained* elevation of venous pressure must be balanced by a supporting increase in tissue pressure³ and this is not easily explained by the theory of brief reduction in cardiac output. Altschule⁴ found the venous pressure to be between 8 and 71 cm. saline in seven of fifteen patients with cardiac edema whereas normal subjects showed pressures below 10. We have made similar observations using direct atrial pressure readings in edematous subjects⁵ so that the objections often raised to measurements using peripheral veins would seem to be answered. Venous pressures as high as 50 cm. saline, without demonstrable edema, have been recorded by Burch and Ray^{6a} in patients following ligation of the inferior vena cava. In addition to this several cardiac patients have been reported with venous pressures as high as 16 to 31 cm. water without visible edema.^{6b} We have seen one individual with constrictive pericarditis and one with chronic heart failure with atrial

pressures of 23 cm. and 27 cm., respectively; the first patient never had edema and the second was edema-free at the time of the measurement. Thus it is evident that there is little correlation between the presence of edema and the level of venous pressure. Starr⁷ measured the "static" venous pressure in patients with heart failure immediately after death and found it elevated even after the heart had stopped beating. He also showed⁸ in dogs that almost complete destruction of the right ventricle with a cautery resulted in no elevation of venous pressure. These experiments suggest that right ventricular failure *per se* has little to do with elevated venous pressure. The second of the two intimates that the left ventricle may be capable of carrying practically all of the circulatory load in dogs at rest. In mentioning "right ventricular failure" one must bear in mind that the left ventricle can pump only as much blood as passes through the right ventricle, so that when the right ventricle "fails" the left must also fail. Landis⁹ demonstrated that fluid accumulated in the tissues with venous pressures of 15 to 20 cm. water. However, he used a tourniquet applied above the elbow which would also produce lymphatic obstruction.

If interference with lymph flow were implicated, one would expect a relatively high protein content of the edema fluid since one of the functions of the lymph vessels is to return protein to the blood stream. Stead and Warren¹⁰ found the average protein content of cardiac edema

* This work was supported by grants from the Office of Scientific Research and Development; Smith, Kline and French Laboratories; Life Insurance Medical Research Fund. and the U. S. Public Health Service.

fluid to be quite low (average 0.24 Gm. per cent) in fourteen patients. In our opinion this also indicates that capillary permeability is not appreciably increased as the relative proportion of protein to water should be greater in subjects with increased capillary permeability, although some disagree.¹¹ Stead and Warren¹² studied two patients with chronic congestive heart failure who had been freed of edema by the use of sodium restriction and mercurial diuretics. These patients had exhibited consistent signs of heart failure over a long period of time, had regular rhythm and both had cardiac outputs well below average.¹³ As salt was added to the diet in amounts easily eliminated by normal subjects, the patients had an increase in weight and blood volume which definitely preceded the rise in venous pressure. Harrison, Reichsman and Grant¹⁴ gave evidence which seemed at variance with these findings. Patients with auricular fibrillation who were fully digitalized were taken off digitalis and allowed to fibrillate at a rapid rate. In their patients a rise in venous pressure preceded the weight gain. However, these authors most likely were dealing with patients with a changing cardiac output. An individual with a stabbed heart and pericardial tamponade with a sudden fall in cardiac output may get a rise in venous pressure and hematocrit without change in blood volume (except sometimes a slight decrease associated with the venous pressure rise) supposedly due to capillary or venous constriction. Arteriolar constriction *per se* would hardly account for this change. Cooper, Stead and Warren demonstrated this phenomenon in dogs.¹⁵ A similar mechanism was probably involved in the experiments of Harrison, Reichsman and Grant. Lyons¹⁶ gave large amounts of sodium salts to normal individuals. The weight and blood volume rose simultaneously and finally the venous pressure became elevated. This indicates that when the body receives more salt than the kidney can excrete, salt and water are retained and the venous pressure rises secondarily.

There can be no question that, in the last analysis, edema of heart failure is the result of failure of the kidney to excrete salt and water normally. That the primary difficulty is with salt and not with water has been demonstrated by many observers.¹⁷⁻²⁰ The sodium ion and not the chloride ion is the one implicated in edema, as sodium bicarbonate produces edema and ammonium chloride causes diuresis.²¹

Futcher and Schroeder²² and Reaser and Burch²³ have demonstrated that the kidney in chronic heart failure is unable to excrete sodium normally. Seymour et al.,² in an effort to explain this, showed a decreased renal plasma flow (PSP clearance) and filtration rate (inulin clearance) in patients with heart failure, with return toward normal after digitalization. They attributed these changes to the elevated venous pressure as the fall in venous pressure with digitalis was accompanied by improvement in renal function. It should be pointed out, however, that they were dealing with a third variable—the cardiac output—which they showed to increase with digitalis. Much confusion about cardiac output in heart failure has arisen from a failure to recognize that the resting cardiac outputs which have been measured in the past are of significance only in subjects who have heart failure at rest. In these individuals the cardiac output is consistently low.

Studies were made in our laboratory on patients with both "acute" and "chronic" heart failure using hippurate and inulin clearances,^{24,25} cardiac outputs employing the direct Fick principle^{26,27} and some atrial pressures measured through a catheter lying in the right atrium.²⁸ The "chronic" patients were those who had fixed heart failure at bed rest. This usually does not change when the patient is relieved of his signs of congestive failure by the only means possible—either rigid sodium restriction or the use of mercurial diuretics. The patients with so-called "acute" failure have normal resting cardiac outputs but are able to increase the cardiac output very little with exercise.²⁹ In other words, they are the

patients with a low cardiac reserve. In the group with a low cardiac output the renal plasma flow was reduced from one-third to one-sixth normal, whereas the cardiac output was seldom less than one-half normal. Thus the kidney was receiving on an average of 8 to 10 per cent of the cardiac output instead of its usual 20 to 25 per cent. This suggests a shunt away from the kidney produced either by relative intrinsic vasoconstriction in the kidney or by relative vasodilatation in other parts of the body. Also, the filtration rate remained within normal limits or slightly below until the renal plasma flow was about 200 cc. per minute or less (normal 600 to 700 cc./min.). This was probably accomplished by a rise in filtration pressure produced by constriction of the efferent arteriole of the glomerulus. Thus the fraction of renal plasma flow filtered (filtration fraction) was as high as 40 to 60 per cent, the normal being about 20 per cent.

By dividing patients into "chronic" and "acute" groups according to whether or not they required mercurial diuretics for compensation and by studying their inulin clearances, the "critical" filtration rate for sodium retention was found to be about 70 cc. per minute.³⁰ However, these patients were not at absolute bed rest and some of them might not have required mercurials if they had been. Therefore, it is possible that the level should be somewhat lower. There was a distinct correlation between the severity of symptoms and the level of filtration rate. This does not prove that the low filtration rate is the cause of the sodium retention as each might be an unrelated phenomenon set in motion by a common cause.

It has been shown that renin produces efferent arteriolar constriction³¹ and it is well known that renin production is increased in subjects with a low cardiac output. Renin is not demonstrable in blood coming from the kidney of normal individuals but it was demonstrated in the renal vein blood of eight of ten patients with heart failure. No renin was found in the arte-

rial blood of patients with heart disease.³² However, the bio-assay technic employed dogs. While this is adequate to determine an increased concentration of renin, a more sensitive method is needed to decide whether there is an absolute increase or simply the same amount secreted into the reduced amount of blood flowing through the kidney. If renin production is increased, it offers a possible explanation for the mechanism of arteriolar constriction and perhaps venoconstriction seen in heart failure, as renin is known to produce such effects.³³

We also found a decreased excretion of sodium in patients with heart failure which was roughly proportional to the decrease in filtration rate and we explained the sodium retention on this basis. We believed at the time that the tubules continued to reabsorb sodium because of their "fundamental sodium-conserving function," although it was admitted that other causes might exist.²⁸ Mokotoff, Ross and Leiter³⁴ showed that sodium reabsorption paralleled sodium filtration in heart failure and gave a mathematical formula, reabsorption of sodium = filtration rate x plasma sodium, representing this relation. This does not reveal the cause of sodium retention in heart failure, as sodium filtration and sodium reabsorption are such large quantities as compared with sodium excretion that the latter could be multiplied several times without affecting the formula appreciably. One is forced to conclude, as Newburgh and Leaf³⁵ have done, that an evaluation of the role of the filtration rate in sodium excretion cannot be made directly because sodium excretion is so small and the errors in the inulin determination of filtration rate are so large. Indirect evidence is given below.

To determine whether the same principle of low filtration rate applied to patients with a normal resting circulation, it was necessary to study them in the exercising state since their failure occurs only under such conditions. We²⁹ found that six of ten cardiac subjects showed a fall in filtration rate to the "critical" level of 70 cc./minute

when they performed mild exercise roughly equivalent to walking leisurely on level ground. Sodium excretion was markedly diminished in two cardiac subjects who had a fall in filtration rate with exercise and not in a cardiac patient whose filtration rate

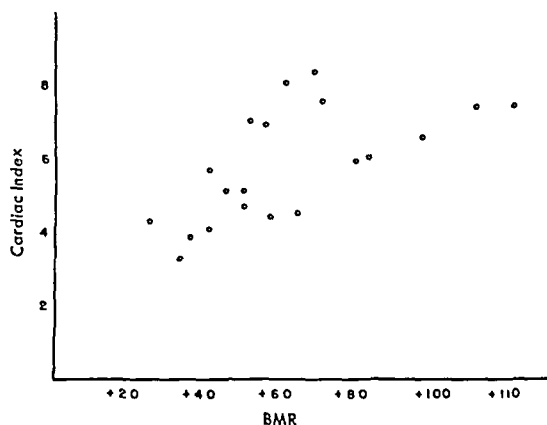


FIG. 1. Note that the cardiac index increased in direct proportion to the BMR. (Courtesy of Dr. E. S. Brannon.)

did not decrease with exercise. This seemed to fall in line with our hypothesis. But Kattus et al.³⁶ demonstrated a fall in sodium excretion with exercise in normal subjects who had no decrease in filtration rate although they did find a somewhat greater decrease in sodium excretion in their cardiac subjects who had a diminished filtration rate with exercise. It appears that there may be a mechanism for sodium retention during exercise which is partially if not entirely independent of the filtration rate. As already pointed out, the errors in inulin clearance are great and Kattus³⁶ studies can be evaluated better when the data are published in detail.

The foregoing experiments do not account for the patients who have heart failure with high resting cardiac outputs such as those with anemia, thyrotoxicosis and beri-beri. Heart failure is rare in resting anemic subjects with normal kidneys and no heart disease. Bradley³⁷ found that anemia results in a low renal blood flow. We⁵ found that the renal blood flow is reduced but the renal plasma flow is relatively normal except in very severe anemia because of the relatively high proportion of plasma in anemic blood. The filtration rate

is unaffected. In thyrotoxicosis the cardiac output varies directly with the basal metabolic rate. (Fig. 1.) All those with heart failure have a high cardiac output. Most of those who have congestive heart failure exhibit slight increases in the cardiac output

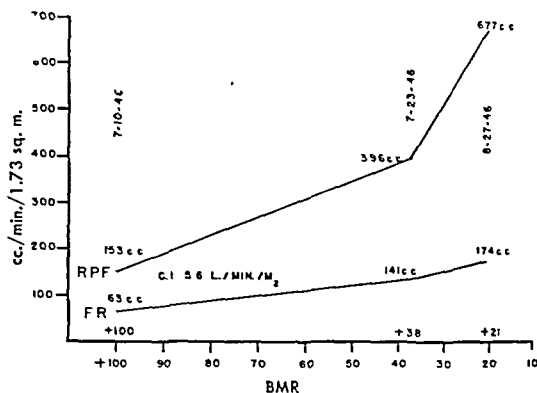


FIG. 2. Despite the high cardiac index the renal plasma flow and filtration rate are decreased to one-fourth and one-half normal levels, respectively. As the BMR fell and the renal plasma flow rose above 200 cc./min., the filtration rate rapidly became normal. The renal plasma flow approached normal more gradually.

as they become compensated, suggesting that a slight decrease occurs as they go into failure.³⁸ Most of them become compensated at absolute bed rest. These have a normal or high renal plasma flow and filtration rate.³⁹ Occasional patients continue to have failure at rest. We have studied one of these and the results are shown in Figure 2. Both renal plasma flow and filtration rate were reduced just as in other cases of chronic congestive failure despite the high cardiac index (cardiac index = cardiac output per square meter body surface). As the BMR fell with administration of Lugol's solution and propylthiouracil, the filtration rate rose sharply and the renal plasma flow increased at a somewhat slower rate. Obtaining multiple data on the cardiac output was impossible because of limited veins of sufficient size, but it is fair to assume that the cardiac output fell as the BMR fell just as it did in Brannon's patients.

Thus we find that as the metabolic demands of the tissues decrease the renal plasma flow and filtration rate rise in severe thyrocardiac patients. Since the metabolic demands of the tissues become greater in

exercise, the renal plasma flow decreases. This decrease is greater in cardiacs than in normal subjects and the former also have a fall in filtration rate. Since cardiac subjects have only limited ability to increase the cardiac output with exercise, it appears from these data that when the patient cannot increase his cardiac output sufficiently for tissue metabolic needs the kidney shuts down. The kidney functions fairly adequately until its blood supply decreases to about 20 per cent of normal.^{40,41} The shunting of blood to more delicate tissues such as the brain may be a very useful thing in times of stress such as shock and heart failure.

The mechanism of renal shutdown in response to an "inadequate" cardiac output is of great interest because knowledge of it may throw light on some of the fundamental processes in heart failure. Several possibilities exist. It could be under sympathetic control, it could be mediated through one of the renal hormones or it might be set off by some other hormone or metabolite.

It is known⁴² that cardiac output may drop as much as 20 per cent if an individual stands motionless at an angle of 60 degrees with the horizontal. The renal plasma flow and filtration rate diminish proportionately.⁴³ This phenomenon resembles what happens in heart failure except that Smith has found the filtration fraction to be normal as a result, he suggests, of afferent arteriolar constriction. However, the filtration fraction (per cent of renal plasma flow which is filtered, normally 20 per cent) may be low because of the fall in blood pressure which occurs.

To test the role of the sympathetic nervous system in these phenomena we⁴⁴ tilted a patient with hypertension who had had a Smithwick sympathectomy. Absence of sweating indicated that the sympathetic nervous system had not regenerated. Despite the loss of sympathetic innervation the same changes in renal hemodynamics occurred as in the normal individual. This was true, too, of a patient with orthostatic hypotension who also failed to sweat below

the fourth dorsal segment. Neither patient had a significant fall in blood pressure so the renal changes cannot be attributed to that.

Further evidence that the sympathetic nervous system is not involved was obtained by producing spinal anesthesia above the fifth dorsal segment in three subjects with congestive failure and diminished renal plasma flow. No increase in renal plasma flow was effected.^{44,45} Since the possibility existed that the kidney blood flow could not increase after so prolonged a shutdown, we gave them 0.72 Gm. aminophylline intravenously to increase the cardiac output.^{46,47,48} The cardiac output rose from 100 to 300 per cent and the renal plasma flow increased as much as 40 per cent without very much rise in blood pressure. In addition to this the fact that the renal plasma flow returned to normal in the thyrotoxic patient described above points to its ability to do so in other types of failure. Thus, the sympathetic nervous system is fairly effectively eliminated.

As mentioned above, renin is found in the renal venous blood of cardiac subjects and not in that of normal individuals. One cannot exclude renin as the cause of these phenomena but the evidence for it is not conclusive.

The posterior pituitary secretion could cause the reduction in renal plasma flow. The great difficulty in assessing its role is that the substances secreted by the pars intermedia of the pituitary are not known. Pitressin, pitocin and pituitrin all may well be artificial substances created by the chemicals used in their isolation. Therefore direct experimentation with these materials might have little significance.

Five patients who stood motionless at a 60 degree angle with the horizontal had striking decreases in the renal plasma flow and filtration rate, with a marked fall in sodium or chloride excretion. (Table 1.) The latter persisted for the period following the return to a horizontal position in one patient in which it was measured and in all of Brun's patients.⁴⁹ The plasma flow did not

return to normal for fifteen or more minutes. Blood from Brun's patients produced marked decrease in urine volume in the recipients. The urine chloride excretion per minute was decreased in one patient and remained the same in another. The renal plasma flow and

what the sodium excretion and renal plasma flow did in the patients with diabetes insipidus because it would assist in determining the cause of the various phenomena which occur in the kidney with motionless standing and might help to define the role

TABLE I
THE MECHANISMS OF SALT AND WATER RETENTION IN HEART FAILURE

Patient	Diagnosis	Position	Time (min.)	Renal Plasma Flow	Filtration Rate	Filtration Fraction	Urine Volume	Sodium Excretion	Concentration Sodium Reabsorbate
				ml. per 1.73 sq.m. per min.		per cent	ml. per min.	m.Eq. per 1.73 sq.m. per min.	m.Eq. per L.
W. M. R.	Normal	Flat	10.0	564	140	24.9	13.2		
			10.1	579	144	24.9	14.1	.164	165.5
			9.9	548	131	23.9	14.4	.168	168.8
		Tilted	15.0	437	119	27.3	10.1	.117	163.5
			15.0	379	113	29.7	5.26	.028	147.0
K. D.	Diabetes (controlled)	Flat	10.2	481	121	25.2	10.2		
			10.1	467	109	23.4	10.6	.128	158.0
			9.7	455	109	24.0	10.9	.131	158.5
		Tilted	15.0	373	112	29.9	10.0	.099	157.0
			15.0	226	72	31.8	4.4	.024	151.7
C. P.	Asymptomatic neurosyphilis	Flat	15.0	868	147	16.9	5.9		
			15.0	746	148	19.8	10.6	.222	157.1
			15.0	763	133	17.5	12.1	.193	161.1
		Tilted	14.8	558	121	21.7	8.6	.108	155.0
			15.2	255	63	24.6	1.6	.016	148.6
			15.4	386	89	23.0	0.39	.027	145.7
J. M. W.	Gonococcal arthritis (convalescent)	Flat	15.0	706	138	19.5	10.0		
			15.0	718	124	17.3	11.2		
			15.0	664	129	18.6	10.7	.107	159.5
		Tilted	15.0	522	134	25.7	9.7	.082	156.6
			15.0	398	121	30.7	5.46	.022	146.7
			15.0	504	120	23.7	4.07	.015	146.0
D. L. D.	Asymptomatic neurosyphilis with serologic relapse	Flat	14.0	641	138	21.5	6.2		
			15.0	556	127	22.8	9.0	.165	158.3
			15.0	496	135	27.1	9.55		
		Tilted	15.0	526	127	24.1	9.8	.144	159.8
			15.5	463	114	24.6	5.75		
			14.5	417	107	25.2	2.1	.061	149.5

filtration rate were not measured in the recipient. These authors believed that some of the changes were produced by the posterior pituitary because less pronounced changes occurred in patients with diabetes insipidus. It would be interesting to know

of the posterior pituitary in heart failure. With the data at hand it is not possible to make any definite statement.

The possibility that increased adrenal cortical secretion might cause the fall in renal plasma flow in heart failure has been

suggested. This seems unlikely since Hellman et al.⁵⁰ showed that the adrenocorticotrophic hormone will increase the renal plasma flow when the latter is diminished in Simmonds' disease. We⁵¹ have given adrenocorticotrophic hormone to two normal subjects without any appreciable change in renal plasma flow or filtration rate. Also, White, Heinbecker and Rolf⁵² have demonstrated that adrenal cortical extract plus desoxycorticosterone acetate will partially alleviate the reduction in renal plasma flow and filtration rate in adrenal deficient dogs. However, they did not increase the diodrast T_m which was also low. The diodrast T_m is not reduced in constrictive pericarditis with heart failure.⁵³ Furthermore, in Addison's disease the filtration rate is reduced to a greater degree than the renal plasma flow, whereas the reverse is true in heart failure whether the venous pressure is high or normal. Evidence will be given below for a marked increase in adrenal cortical secretion. This eliminates the possibility that a deficiency of that hormone plays a part in heart failure. Neither can the increase be responsible for the renal plasma flow changes for the reasons already given.

White, Heinbecker and Rolf have eliminated increased or decreased thyroid and ovarian secretion as the cause of the type of renal change seen in heart failure. They were not able to rule out a decrease in a special "renotropic" hormone in the anterior pituitary. Deficiency of such a substance offers an attractive hypothesis, as it might be more or less automatically reduced in concentration by a fall in cerebral blood flow. No positive evidence of such a substance has appeared thus far although certain negative evidence points to its existence.⁵²

For the sodium retention in heart failure several possible causes exist. The sympathetic nervous system seems effectively ruled out. The filtration rate as a mechanical factor may be important. The clinical relationship between salt retention and the level of filtration rate has already been shown, although it is true that both could

be due to some other related or common cause. In acute glomerulonephritis salt and water retention may occur, presumably due to a low filtration rate. If adrenal cortical hyperactivity could be ruled out, this offers a particularly good situation for demonstrating the importance of filtration in sodium excretion. Conn has shown that the sweat sodium is a good index of the activity of the sodium-retaining hormone of the adrenal cortex. The sweat sodium is low in Cushing's disease (hyperactivity of the adrenal cortex) and high in Addison's disease (low activity of the adrenal cortex). No overlapping was demonstrated. We have found the sweat sodium to be normal in four of five cases of acute glomerulonephritis with edema⁵⁵ and low in the fifth patient. Thus, the normal sweat sodium concentration constitutes good evidence that the adrenal cortex plays no consistent role in the sodium retention of acute glomerulonephritis and suggests that reduced filtration rate may result in salt and water retention. Further evidence is needed before this can be considered settled. A patient with rheumatic heart disease and chronic heart failure was followed for three years with four different series of renal studies and consistently had a moderate reduction in renal plasma flow to 348 and a striking reduction in filtration rate to 49 cc. per minute. The low filtration fraction is the reverse of what is expected in heart failure and it was thought that she had a healed glomerulonephritis with the low filtration rate which may accompany it.^{56,57} Ordinarily sodium retention does not occur in heart failure at rest with a renal plasma flow above 200 to 225 cc. per minute. The fact that in spite of the above this patient had to have mercurial diuretics twice a week, although she did no work, points to a filtration factor operating in her sodium retention. One other patient with a renal plasma flow of 253 cc. per minute and a filtration rate of 65 cc. per minute with a normal sweat sodium also had chronic sodium retention. This patient had been studied twice, with the same results. These

findings again indicate a filtration element in the sodium retention of heart failure. The fact that a very low renal blood flow and filtration rate may occur in renal disease without edema is not opposed to this idea. In renal disease the tubules may also be damaged and unable to handle sodium normally,^{58,59} whereas in heart failure most tubular functions other than diodrast T_m are normal.^{2,40}

We now have four patients, three with low filtration rates and chronic heart failure who have very low sweat sodium concentrations.⁶⁰ Five subjects with less severe failure with relatively normal filtration rates have normal or high sweat sodium concentrations, indicating that the adrenal cortex comes into play in heart failure very late. We were unable to demonstrate any appreciable change in the sweat sodium concentration with exercise. Thus hypoactivity of the adrenal cortex cannot account for relatively normal resting renal blood flow and filtration rate in patients with heart failure, although it may be that there is a lag between stimulation of the adrenal cortex and the change in sweat sodium concentration. It is likely also that adrenal cortical stimulation occurs in coryza and other infections and injuries which are known to increase failure in the cardiac patient. In fact the sweat sodium of one severe cardiac patient with a low sweat sodium fell to one-half its previous level when the patient developed a skin infection of the cubital fossa.⁵¹

One more possibly major factor will be considered in the edema of heart failure—the antidiuretic hormone of the pituitary. It is not believed that this alone can produce sodium retention, and water retention *per se* does not usually produce edema. However, if a severe cardiac subject is rendered partially free of edema with mercurial diuretics, he may then become apparently unresponsive to mercurial diuretics. If mercurial diuretics are continued, the blood sodium will gradually fall. In one of our patients it reached a value of 118 m.Eq./L. and in another 114 m.Eq./L.

(our normal = 137 to 143 m.Eq.). Despite this, in both no water diuresis occurred although sodium excretion was increased about tenfold and she was still edematous. Several possibilities exist to explain this: the antidiuretic hormone of the posterior pituitary could be responsible; the normal balance between the proximal and distal convoluted tubules could be disturbed by the mercury which apparently acts on the proximal convoluted tubules only; or it is possible that a disturbance in intracellular electrolyte metabolism may be involved. It is not definitely known that such a disturbance can produce edema. That intracellular electrolyte imbalances may enhance heart failure has been demonstrated in animals. Desoxycorticosterone may cause sodium retention with potassium loss producing areas of myocardial necrosis and heart failure.^{61,62} The same thing is thought to occur in other types of sodium retention and potassium deficiency and could occur in a cardiac subject with sodium retention and superimposed potassium deficiency due to nausea and low intake. In such states the patient may become irrational. In cardiac delirium relief of massive edema with diuretics usually produces improvement. This is probably not due to improvement in cerebral circulation since the cardiac output does not change appreciably under these circumstances. The change could be caused by correction of an intracellular electrolyte imbalance.

The question is frequently asked, Is salt and water retention useful in heart failure or is it an error of metabolism? Landis⁶³ thinks that it is beneficial in the standing cardiac subject but that it may be dangerous when the patient lies down. Starling,⁶⁴ Borst⁶⁵ and McMichael⁶⁶ all believe it to be a good thing and essential to maintenance of the cardiac output or the most favorable blood volume possible under the circumstances. They all accept the thesis that cardiac output is very sensitive to the level of atrial filling pressure, increasing as the latter increases until severe failure sets in at which time the cardiac output falls. Within

wide limits Warren, Stead, Weens and Brannon^{67,68} have been unable to demonstrate this relationship. Marked increases in atrial pressure as a result of rapid saline infusions and marked decreases from rapid withdrawal of venous blood did not change the cardiac output. For this reason we are inclined to take the view that salt and water retention is an error of metabolism. We believe that the renal blood flow shutdown mechanism and salt and water retaining mechanisms may be useful in combatting the low cardiac output of shock or perhaps simply in assisting in the adjustments to the low cardiac output of standing. In these cases a low cardiac output does result from a low circulating blood volume and salt and water retention would be useful. In cardiac failure low cardiac output results from intrinsic heart disease and we should not expect the rise in venous pressure to change this condition. As a matter of fact, elimination of excess salt and water and high venous pressure with mercurial diuretics produces no appreciable change in cardiac output and renal hemodynamics of the patient. Furthermore, clinically the patient seems greatly improved and no inconvenience is noted in either the horizontal or vertical position. The nearer the blood volume and venous pressure are brought to normal, the better the patient feels although his cardiac output remains essentially the same. One would expect him to feel worse if the rise in blood volume and venous pressure were useful.

SUMMARY

The concept is proposed that edema in heart failure is caused by retention of salt and water produced by a diminished ability of the kidney to excrete salt and water. This disturbance in the kidney is the result of an inadequate cardiac output which is both *relatively* and *absolutely* reduced in patients who have chronic cardiac edema at rest, and is *relatively* reduced as compared with general or specialized tissue demands in other cardiac subjects with edema, i.e., those who fail with exertion, hyperthyroid-

ism, anemia or beri-beri, and who may have a normal or elevated resting cardiac output. The inadequate cardiac output, through one or more mechanisms, causes the kidney to excrete less salt and water. It also produces a reduction in renal plasma flow and filtration rate by a contraction of the efferent arterioles of the kidney effected by some humoral substance. The reduced filtration rate corresponds closely to the reduction in sodium excretion and evidence is presented which indicates that the lowered filtration rate may be one of the causes of the reduction in sodium excretion. In advanced stages of heart failure the reduction in salt and water excretion is probably produced by at least two other means—the adrenal cortex is definitely stimulated and the pars intermedia of the pituitary probably also plays a part. Much work needs to be done to evaluate the role of these various factors both in renal hemodynamics and sodium excretion. Too little is known of the effect of changes in the intracellular electrolytes on edema formation and cardiac physiology to warrant any speculation as to the part taken by them.

Acknowledgment: Technical assistance was given in this work by Marguerite A. Borders, Eloise Cavin and Sarah D. Hutchins.

REFERENCES

1. GIBSON, J. G. and EVANS, W. C., JR. Clinical studies of the blood volume, changes in blood volume, venous pressures, and blood velocity rates in chronic congestive heart failure. *J. Clin. Investigation*, 16: 851, 1937.
2. SEYMOUR, W. B., PRITCHARD, W. H., LONGLEY, L. P. and HAYMAN, J. M., JR. Cardiac output, blood and interstitial fluid volumes, total circulating serum protein and kidney function during cardiac failure and after improvement. *J. Clin. Investigation*, 21: 229, 1942.
3. WARREN, J. V., MERRILL, A. J. and STEAD, E. A., JR. Role of the extracellular fluid in the maintenance of blood volume. *J. Clin. Investigation*, 22: 635, 1943.
4. ALTSCHULE, M. D. The pathological physiology of chronic cardiac decompensation. *Medicine*, 17: 75, 1938.
5. MERRILL, A. J. Unpublished data.
6. (a) BURCH, G. and RAY, T. Proc. Am. Fed. Clin. Research, Southern Section, 1944. (b) SWIRE, F. H. *Clin. Sc.*, 2: 317, 1935.

7. STARR, I. Role of the "static blood pressure" in abnormal increments of venous pressure especially in heart failure. *Am. J. M. Sc.*, 199: 40, 1940.
8. STARR, I. The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease. *Am. Heart J.*, 26: 291, 1943.
9. KROGH, A., LANDIS, E. M. and TURNER, A. H. The movement of fluid through the human capillary walls in relation to venous pressure and to the colloid osmotic pressure of the blood. *J. Clin. Investigation*, 11: 63, 1932.
10. STEAD, E. A., JR. and WARREN, J. V. The protein content of the extracellular fluid in normal subjects after venous congestion and in patients with cardiac failure, anoxemia, and fever. *J. Clin. Investigation*, 23: 283, 1944.
11. WOOD, B. In MacBryde, C. M., Signs and Symptoms; Their Clinical Interpretation. P. 232. Philadelphia, 1947. J. B. Lippincott Co.
12. WARREN, J. V. and STEAD, E. A., JR., Fluid dynamics in chronic congestive heart failure. *Arch. Int. Med.*, 73: 138, 1944.
13. WARREN, J. V. and STEAD, E. A., JR. Unpublished data.
14. HARRISON, T. R., REICHSMANN, F. and GRANT, H. Some observations on the pathogenesis of cardiac edema. *Tr. A. Am. Physicians*, 59: 51, 1946.
15. COOPER, F. W., STEAD, E. A., JR. and WARREN, J. V. The beneficial effect of intravenous infusions in acute pericardial tamponade. *Ann. Surg.*, 120: 822, 1944.
16. LYONS, R. H., JACOBSON, S. D. and AVERY, N. L. Increases in the plasma volume following the administration of sodium salts. *Am. J. M. Sc.*, 208: 148, 1944.
17. SCHROEDER, H. A. Studies on congestive heart failure: I. The importance of restriction of salt as compared to water. *Am. Heart J.*, 22: 141, 1941.
18. PROGER, S., GINSBERG, E. and MAGEDANTZ, H. Effects of ingestion of excessive amounts of sodium chloride and water on patients with heart disease. *Am. Heart J.*, 23: 555, 1942.
19. SCHEMM, F. R. A high fluid intake in the management of edema, especially cardiac edema. I. The details and basis of the regime. *Ann. Int. Med.*, 17: 952, 1942.
20. GORHAM, L. W., LESTER, D. E., WOLF, A. V. and SHULTZ, H. H. The relative importance of dietary sodium chloride and water intake in cardiac edema. *Tr. A. Am. Physicians*, 60: 192, 1947.
21. GOODMAN, L. S. and GILMAN, A. The Pharmacological Basis of Therapeutics. New York, 1941. The Macmillan Co.
22. FUTCHER, P. H. and SCHROEDER, H. A. Studies on congestive heart failure: II. Impaired excretion of sodium chloride. *Am. J. M. Sc.*, 204: 52, 1942.
23. REASER, P. B. and BURCH, G. E. Radioactive tracer studies in congestive heart failure. *Proc. Soc. Exper. Biol. & Med.*, 63: 543, 1946.
24. SMITH, H. W. Personal communication. GOLDRING, W. and CHASSIS, H. Hypertension and Hypertensive Disease. New York, 1944. Commonwealth Fund.
25. SMITH, H. W., GOLDRING, W. and CHASSIS, H. The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney. *J. Clin. Investigation*, 17: 263, 1938.
26. COUNAND, A., RILEY, R. L., BRÉED, E. S., BALDWIN, E. DE F. and RICHARDS, D. W. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. *J. Clin. Investigation*, 24: 106, 1945.
27. PADILLA, T., COSSIO, P. and BERCONSKY, I. Sondeo del corazon. *Semana méd.*, 2: 391, 445 and 645, 1932.
28. MERRILL, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema. *J. Clin. Investigation*, 25: 389, 1946.
29. HICKAM, J. B. and CARGILL, W. H. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and emphysema. *J. Clin. Investigation*, 27: 10, 1948.
30. MERRILL, A. J. and CARGILL, W. H. The effect of exercise on the renal plasma flow and filtration rate of normal and cardiac subjects. *J. Clin. Investigation*, 27: 272, 1948.
31. MERRILL, A. J., WILLIAMS, J. R. and HARRISON, T. R. The site of action of the renal pressor substance. *Am. J. M. Sc.*, 18: 196, 1938.
32. MERRILL, A. J., MORRISON, J. and BRANNON, E. S. Concentration of renin in renal venous blood in patients with chronic heart failure. *Am. J. Med.*, 1: 468, 1946.
33. BRADLEY, S. E. and PARKER, B. The hemodynamic effects of angiotonin in normal man. *J. Clin. Investigation*, 10: 715, 1941.
34. MOKOTOFF, R., ROSS, G. and LEITER, L. Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. *J. Clin. Investigation*, 27: 1, 1948.
35. NEWBURGH, L. H. and LEAF, A. Personal communication.
36. KATTUS, A., SINCLAIR-SMITH, B., GENEST, J. and NEWMAN, E. V. The renal tubular reabsorption of salt with exercise in a patient with cardiac failure and normal controls. *Proc. Am. Soc. Clin. Investigation. J. Clin. Investigation*, 27: 542, 1948.
37. BRADLEY, S. E. and BRADLEY, G. P. Renal function during chronic anemia in man. *Blood*, 2: 192, 1947.
38. BRANNON, E. S. and WEENS, H. S. Hemodynamics and roentgenologic studies of patients with pulmonary hypertension. *Proc. Am. Fed. Clin. Research, Southern Section*, 1945, Atlanta.
39. MERRILL, A. J. and CARGILL, W. H. Mechanism of edema formation in thyrotoxic heart disease. *Proc. Southern Soc. Clin. Research. Am. J. Med.*, 3: 502, 1947.
40. WARREN, J. V., BRANNON, E. S. and MERRILL, A. J. A method of obtaining renal venous blood in unanesthetized persons with observations on the extraction of oxygen and sodium para-aminohippurate. *Science*, 100: 108, 1944.
41. (a) VAN SLYKE, D. D. Personal communication.
(b) DOLE, V. P., EMERSON, K., JR., PHILLIPS, R. A., HAMILTON, P. B. and VAN SLYKE, D. D. The renal

- extraction of oxygen in experimental shock. *Am. J. Physiol.*, 145: 3, 1946.
42. STEAD, E. A., JR., WARREN, J. V., MERRILL, A. J. and BRANNON, E. S. Cardiac output in male subjects as measured by the technique of right atrial catheterization: normal values with observations on the effect of anxiety and tilting. *J. Clin. Investigation*, 24: 326, 1945.
 43. SMITH, H. W. Lectures on the Kidney. Lawrence, Kansas, University of Kansas Extension Division, 1943.
 44. TURNER, H., JAMES, D. F. and MERRILL, A. J. Studies on the mechanism of reduction in renal blood flow in heart failure; preliminary report. *Proc. Am. Fed. Clin. Research. Am. J. Med.*, 5: 619, 1945.
 45. MOKOTOFF, R. and ROSS, G. The effect of spinal anesthesia on the renal ischemia in congestive heart failure. *J. Clin. Investigation*, 27: 335, 1948.
 46. STARR, I., GAMBLE, C. J., MARGOLIES, A., DONAL, J. S., JR., JOSEPH, N. and EAGLE, E. A clinical study of the action of 10 commonly used drugs on cardiac output, work and size; on respiration, on metabolic rate and on the electrocardiogram. *J. Clin. Investigation*, 16: 799, 1937.
 47. HOWARTH, S., McMICHAEL, J. and SHARPEY-SCHAFER, E. P. The circulatory action of theophylline ethylene diamine. *Clin. Sc.*, 6: 125, 1947.
 48. ESCHER, D. J. W., WESTON, R. E., LEINER, G., LEITER, L. and GOLDAT, S. The effect of aminophylline on cardiac output and renal hemodynamics in man. *Federation Proc.*, 7: 31, 1948.
 49. BRUN, C., KNUDSEN, E. O. E. and RAASCHON, F. On the cause of post-syncopal oliguria. *Acta med. Scandinav.*, 122: 486, 1945; Kidney function and circulatory collapse, post-syncopal oliguria. *J. Clin. Investigation*, 25: 568, 1946.
 50. HELLMAN, L., WESTON, R. E., ESCHER, D. J. W. and LEITER, L. The effect of adrenocorticotropin on renal hemodynamics and uric acid clearance. *Federation Proc.*, 7: 52, 1948.
 51. MOSELEY, A. J. and MERRILL, A. J. Unpublished data.
 52. WHITE, H. L., HEINBECKER, P. and ROLF, D. Some endocrine influences on renal function and cardiac output. *Am. J. Physiol.*, 149: 404, 1947.
 53. LANDOWNE, M., ALVING, A. S. and ADAMS, W. Renal and total circulation in two cases of constrictive pericarditis. *J. Clin. Investigation*, 21: 626, 1942.
 54. CONN, J. W., LEWIS, L. H., JOHNSTON, M. W. and JOHNSON, B. J. The electrolyte content of thermal sweat as an index of adrenal cortical function. *Proc. Am. Soc. Clin. Investigation. J. Clin. Investigation*, 27: 529, 1948.
 55. HUGHES, D. J., TURNER, H. H. and MERRILL, A. J. Unpublished data.
 56. EARLE, D. P., JR., TAGGART, J. V. and SHANNON, J. A. Glomerulonephritis; a survey of the functional organization of the kidney in various stages of diffuse glomerulonephritis. *J. Clin. Investigation*, 23: 119, 1944.
 57. BLACK, D. A. K., PLATT, R., ROWLANDS, E. N. and VARLEY, H. Renal haemodynamics in acute nephritis. *Clin. Sc.*, 6: 295, 1948.
 58. THORN, G. W., KOEPF, G. F. and CLINTON, M., JR. Renal failure simulating adrenocortical insufficiency. *New England J. Med.*, 231: 76, 1944.
 59. BRADLEY, S. E. The Pathologic Physiology of Uremia in Chronic Bright's Disease. Springfield, Ill., 1948. Charles C. Thomas.
 60. HUGHES, D. J., TURNER, H. H., MOSELEY, A. J. and MERRILL, A. J. Unpublished data.
 61. DARROW, D. C. and MILLER, H. C. Production of cardiac lesions by repeated injections of desoxycorticosterone acetate. *J. Clin. Investigation*, 21: 601, 1942.
 62. GAMBLE, A., WIESE, H. and HANSEN, A. E. Marked hypokalemia in prolonged diarrhea; possible effect on the heart. *J. Pediat.* (In press.)
 63. LANDIS, E. M., BROWN, E., FAUTEAUX, M. and WISE, C. Central venous pressure in relation to cardiac "competence," blood volume and exercise. *J. Clin. Investigation*, 25: 237, 1946.
 64. STARLING, E. H. The Fluids of the Body. London, 1909. Archibald, Constable & Co.
 65. BORST, J. G. G. The maintenance of an adequate cardiac output by the regulation of the urinary excretion of water and sodium chloride: an essential factor in the genesis of oedema. *Acta med. Scandinav.*, Supplement ccvii (207), Vol. 130, 1948.
 66. McMICHAEL, J. Circulatory failure studied by means of venous catheterization. *Adv. Int. Med.*, 1: 64, 1947.
 67. WARREN, J. V., BRANNON, E. S., WEENS, H. S. and STEAD, E. A., JR. Effect of increasing the blood volume and right atrial pressure on the circulation of normal subjects by intravenous infusions. *Am. J. Med.*, 4: 193, 1948.
 68. WARREN, J. V., BRANNON, E. S., STEAD, E. A., JR. and MERRILL, A. J. The effect of venesection and the pooling of blood in the extremities on the atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances. *J. Clin. Investigation*, 24: 337, 1945.

Clinic on Psychosomatic Problems

A Case of Duodenal Ulcer with Anxiety Attacks Treated by Psychotherapy

THE clinics are designed to bring out psychosomatic relationships both in symptomatology of the patient and in the organization of the hospital. Reports are directed by Drs. Stanley Cobb and Allan M. Butler and are edited by Dr. Henry H. W. Miles. This is a report of a staff meeting of the Psychiatric Service of the Massachusetts General Hospital. The preparation of these psychosomatic case histories receives support from the Josiah Macy, Jr., Foundation.

DR. AVERY D. WEISMAN: L. F., No. 518808, a thirty-year old farm worker was admitted to the hospital complaining of attacks of palpitation for the past three months and of epigastric pain previously diagnosed as duodenal ulcer since the age of fifteen.

The first anxiety symptoms occurred while the patient was convalescing in a hospital from a minor back injury which, according to his wife and the family doctor, had been unduly disabling. There was a sudden onset of faintness, palpitation, an "alarming sensation" in his chest and dread of death. The attack lasted two days after which he remained in the hospital three weeks because of a severe headache following lumbar puncture. After discharge he felt too weak to return to work.

During the next two months there were three more severe anxiety attacks, each with the same apprehensiveness and fear of death. An intense desire to defecate preceded and accompanied each spell. With the last episode the patient suddenly fainted. His wife described him as pale and sweaty, with no tonic or clonic movements.

The patient had first noted epigastric pain and a sensation of constriction about the lower chest when he was fifteen years old. The symptoms were relieved by belching and by eating and were definitely related to emotional upsets. A positive diagnosis of duodenal ulcer was made five years later, and for a year he followed a bland diet with relief of symptoms. He then began using alcohol regularly and the ulcer

symptoms recurred. They continued intermittently from that time on, with a number of severe exacerbations including a hemorrhage, in temporal relationship to troubles with his first wife. The patient was hospitalized many times because of his ulcer. One year before the present admission a laparotomy had been performed for suspected perforation but none was found. At that time he had had financial difficulties and his wife had been sick. The patient was aware of the relationship between situations and his ulcer symptoms, saying: "When things go bad, my ulcer goes bad." He had noticed that during the anxiety attacks his abdominal pain disappeared, and this only frightened him more since he interpreted the absence of pain as a sign of imminent death.

Past medical history included the usual childhood diseases and otitis media at the age of fourteen. He had had a large number of accidental injuries and various fractures. Eight years before the present admission he was said to have had pulmonary tuberculosis and was treated by pneumothorax. Subsequent x-rays had all failed to show evidence of an active lesion.

Social history disclosed many factors associated with the patient's symptoms and behavior patterns. He was the youngest of three children born to an alcoholic ne'er-do-well father and a promiscuous mother who separated when the patient was eighteen months old. The elder siblings were sent to foster homes but the patient was placed in a large state institution where

homeless children had to mingle with cretins, epileptics and idiots. He was unhappy and fearful there. He was afraid of the dark and afraid of strangers. He walked in his sleep, had nightmares and enuresis. There were also gastrointestinal symptoms such as anorexia, food-fussiness and vomiting.

In the institution discipline was severe and beatings were customary. When the patient first developed abdominal pain, he did not ask for medical attention for fear of added punishment. He remembered that some of the feeble-minded boys ate in an offensive manner, gulping their food like animals and sometimes drooling into their bowls. At times he became so disgusted, angry and rebellious that his pain increased markedly and he vomited. If seen by an attendant, he was forced to eat his vomitus.

Finally when he was nineteen he got into a fight with an attendant and was trying to kill him when other guards intervened. He then ran away but was soon apprehended. A sympathetic judge paroled him to a farm for two years where he was fairly happy.

At the age of twenty-one he set out to find his parents only to discover that he could not get along with either of them. Then followed a period of wandering about the country doing unskilled labor. For a few weeks he worked for a farmer, becoming very fond of the latter's wife, whom he called "mom." He felt as if he had found a home and was bitterly disappointed when the farmer discharged him. He vowed that someday he would return and take his "mother" to live with him as she had confided that she was unhappy with her husband. Several years later when he returned to New England she left her husband and came to stay with the patient and his wife.

The patient was married when he was twenty-five and was sorry almost immediately. He suspected that his wife was unfaithful but never voiced his suspicions. Eighteen months later he left her without trying to get a divorce. During the brief marriage he was in and out of hospitals

chiefly because of ulcer symptoms and also for injuries sustained at work. After leaving his wife he was depressed and lonely and became a hobo, working only enough to buy liquor which he drank to excess. Stirred by the attack at Pearl Harbor he enlisted in the Marine Corps but was discharged two months later because of the duodenal ulcer. During this brief service he was in trouble for impulsively striking a non-commissioned officer.

He then formed a bigamous relationship with a farm girl who became his common-law wife. They hitch-hiked around the country for a year with no ties and no responsibilities ("the happiest period of my life") and finally settled in New England. They had two children, and after the birth of the second the patient's adopted mother came to live with them. The patient's wife worked and became fairly successful financially while he remained an unskilled laborer.

Physical examination revealed a muscular, well proportioned man who was tense but not acutely ill. The only findings of significance were a right pararectus scar, slight epigastric tenderness and loud peristaltic sounds.

Urinalysis and complete blood count were normal. The Hinton test was negative, and three stools were negative for occult blood. Electrocardiogram and electroencephalogram were considered normal. The basal metabolic rate was -17 . Chest x-ray revealed an area of increased density in the right apex, apparently an old, healed tuberculous infection. X-ray examination of the gastrointestinal tract showed prominent gastric rugae but no evidence of a gastric lesion. The duodenal cap was constantly deformed and a persistent fleck of barium indicated an active ulcer crater.

The patient remained five weeks in the psychiatric ward during which time there were twenty-eight therapeutic interviews of an hour each. In describing the setting of the first anxiety attack the patient brought out feelings of helplessness associated with fear that his back had been injured perma-

nently. He had been worried over his financial straits and had fantasies of wife and children being left destitute should he die. There were also fears that his first wife would locate him and prefer charges of bigamy. A strong feeling of dependence upon his second wife was expressed. The associations then led back to experiences in the institution where the boys were frequently whipped on the buttocks. They were made to line up and bend over, and while waiting his turn the patient sometimes defecated involuntarily. He also recalled that one of the matrons used to punish by inserting a short stick, smeared with laundry soap, into boys' rectums. This produced cramps and defecation. (It is interesting how this material correlated with the desire to defecate associated with the anxiety attacks, and with the patient's impulsive outbursts when startled by an approach from the rear.)

It was pointed out that his feelings of being helpless and afraid in the face of current life situations were associated with the anxiety attack, and that the latter, essentially, was the physical expression of fear, helplessness or apprehensiveness. Further discussion of the anxiety symptoms utilized current material. After an anxiety attack one night in the ward he told of feelings of disappointment that his wife had failed to visit him and his uneasiness because he could not reach her by telephone. His associations went on to fantasies of being attacked by a fearful animal and of being dead. (Being left alone, i.e., "helpless," stirred up his anxiety.)

The ulcer symptoms were then investigated and the patient recalled that his first abdominal pain was associated with fantasies of smashing the skull of a hated gym instructor at the institution. He talked about various men in his life who have tried to put things over on him. "When they seem to be decent, then they fail me." Later he expressed doubts about his treatment and had fantasies that the therapist did not wish to help him. This distrust was discussed in the light of past feelings. His own words

were used to illustrate: "Men I trust put me behind the eight-ball." The patient accepted the interpretation, admitting that consciously he knew his misgivings were unrealistic.

Various periods in his life when the ulcer symptoms had been either severe or in remission were taken up in detail. They were very bad during his first marriage. He knew his wife was unfaithful and he was very unhappy but was unable to do anything until he actually caught her with another man. Then he simply walked out without seeking legal recourse. He endured the unhappy relationship because of a longing for a companion and a home, "things I'd never had before." He also spoke of his adopted mother. "She was the first woman I could ever talk to." He felt well while staying with her and her husband but then the latter became jealous and got rid of him. The ulcer symptoms returned promptly.

A ward incident then furnished utilizable material. He was forbidden to play poker and was much angered by the nurse's "superior attitude"; his ulcer pain returned temporarily. In discussing the incident his associations led back to memories of the institution where he was helpless in the face of brutal authority. (Impotent rage in reaction to the threat of force seemed to be the important emotion.) Interpretation was made that his feeling of being abused led to rage and feelings of insecurity and that these were associated with the ulcer symptoms.

Another time the patient became angry because there was fish for lunch. It was a food he detested and he developed a painful, "tight feeling" in the lower chest. Again the associations led to his disgust with the food at the institution and his impotent anger. It was pointed out to him how in many ways he still reacted emotionally as he did long ago. He accepted this interpretation but then asked: "Why do I do it? Why can't it all come out—and get it over with?"

A number of interviews were devoted to investigation of his numerous hospitalizations and injuries and it seemed clear that

several were escape reactions at times when the patient could not cope with his problems. He told of his sexual experiences and said that he was once supported for three months by a prostitute. The fact that she preferred him to all the other men made him proud of his sexual ability, and it was noted that during this period his ulcer was asymptomatic. He expressed guilt over his behavior during the first marriage, saying that if he "had been a man" he would have insisted on a divorce. He had had fantasies of killing his wife and her lover but actually could not bring himself to do anything at all except walk out. (It was evident that the patient had strong feelings of dependency and could not wholly accept them. When his dependent needs were satisfied, his ulcer symptoms were better; when there was a conflict, the symptoms became worse.)

At this point in therapy the patient was presented at a staff conference. Symptomatically, he had improved considerably although a repeated gastrointestinal series showed the ulcer crater unchanged in size.

Presentation of the Patient. The patient entered the conference room with an air of composure. A slight tremor in the voice and some tenseness of posture were the only evidences of nervousness. Considering his social and economic background his choice of words and manner of speech were remarkably good. He answered questions without hesitation or embarrassment and seemed anxious to make a good impression.

DISCUSSION

DR. JAMES A. HALSTEAD: Has he not had long remissions when his stomach was better?

DR. WEISMAN: He has had a number of periods of security—when he lived with the woman who was his adopted mother, and with his second wife going around the country without responsibility; also at other times when he met older women who supported him. He worked once for an older doctor and was well then.

DR. HALSTEAD: I performed a gastroscopy on him. The mucosa was absolutely

normal; there was no increased redness. About 50 per cent of the people with an active ulcer will show changes of the mucosa. The x-ray does show an active ulcer even though his symptoms are now inactive.

DR. JACOB E. FINESINGER: Did you make any interpretations to him?

DR. WEISMAN: Only by throwing things back at him, reminding him of something he had said before.

DR. EDWARD HITSCHMANN: Such people are described in the literature. They have no ideal in childhood. Usually they develop into psychopaths or occasionally criminals. They have no mother and cannot identify with an honest father. This question is important here; and I fear that unless we hear more about his character and his morals, we will be unable to understand the mechanisms of his neurosis, because these people are not as clearly developed as the usual neurotic who has a conscience or superego. This case is more interesting because ulcer beginning at fifteen is rare. He may now have changed his character so that he is capable of anxiety, self-reproach and guilt feelings. Such cases have been described as finally cured by a kind mother. There are some allusions to this possibility here. With such parents, I would name him a psychopath.

DR. FINESINGER: How did his older brother turn out?

DR. WEISMAN: He seems more reliable than the patient although he gets mixed up in get-rich-quick schemes.

DR. HITSCHMANN: I do not believe that the anxiety is so important. Ask him about his conscience, whether he has guilt feelings.

DR. WEISMAN: His wife objects to his overabundance of guilt. He will go out with another woman and insists on coming home and telling about it. She objects to his little boy attitude of confessing and getting dispensation.

DR. MARIANNA TAYLOR: I should think of him as a psychopath. When you see and hear him he seems effeminate and passive.

DR. FINESINGER: There is a good deal in

that. He plans to go to California to open a gift shop because his wife and adopted mother want it.

DR. HENRY M. FOX: Do you feel that what you have done will hold water when you send him out? How much depends upon his being in the situation of dependence on you?

DR. WEISMAN: When he had been in the ward a week or so he had to return early from a week-end because of anxiety. He was out last week-end and got along very well. He had an argument with a garage mechanic without any anxiety.

DR. FINESINGER: Dr. Weisman tried to get relationships between symptoms and precipitating events. Today the patient is able to see the events associated with the ulcer and with the anxiety episodes. The question is what should be the next step therapeutically? What do you think about a fifteen-year old boy developing an ulcer?

DR. HALSTEAD: It is unusual at fifteen to have an ulcer but not enough to rule it out. I also think he will have recurrences for a long time.

DR. FINESINGER: In our few ulcer patients who have had typical neurosis the ulcer symptoms seemed to increase with anxiety symptoms, but here is one fellow whose ulcer seems to get better when he is anxious.

DR. WEISMAN: It depends upon the kind of anxiety. It is hard for the average individual to know when he is feeling anxiety. Is it not true that anxiety swallows up all sorts of affect and thus may mask a more specific type of emotion?

DR. FINESINGER: The term anxiety is loosely used to describe a variety of conscious feelings. It is also used, especially in psychoanalysis, to designate an unconscious feeling which is inferred to exist from specific actions of the patient. Tension states, feelings of general discomfort, feelings of avoidance, hesitation and frustration are among those considered as anxiety. It may be that intensification of feelings of this kind is associated with exacerbations in ulcer symptoms. We have limited, in this case presentation, the use of the term anxiety to

the alarming sensations, feelings of dread and of fright that usually occur in attacks characterized primarily by cardiovascular symptoms. In anxiety attacks the sensations may be so disturbing and the patient's attention focussed on them to such a degree that more subtle types of emotion are not experienced and reported. I believe that is the sequence of events occurring in this patient.

DR. BERNARD BANDLER: My feeling about the anxiety is that it may be prodromal to a psychosis, possibly to alcoholic psychosis. If he did have one, he might have hallucinosis with emphasis on paranoid features. In terms of therapy, as long as Dr. Weisman continues with him, he should do fairly well. The danger is that he may be separated from the doctor. As long as he has confidence in his doctor he will continue to be better.

DR. HERBERT BARRY: This man has at least two and probably three disparate conditions. He has a typical psychopathic personality, almost a textbook picture. As such his statements must all be suspected. Psychopaths are notorious liars. The prognosis is bad. He will go to California and lose track of therapy and get into difficulties. He also has an ulcer. The third thing he has is anxiety neurosis which might be incipient psychosis. The attacks of anxiety are the chief reason he has been willing to stay on the ward. I would not be too hopeful about the outcome.

DR. FINESINGER: His is a complicated case. The striking thing is that this man up to a few months ago did not have frank anxiety symptoms. As to personality, I believe as we all do that he tends to the psychopathic side of the scale. Psychopathic personalities are usually characterized by the absence of feelings of guilt, even in the amount necessary for normal social conformity. The lack of guilt is explained by the failure of the patient to identify in childhood with parents or other figures who furnish ideals for social behavior. This may be due to a disturbance in the capacity for identification or to the absence of suitable

figures in the childhood environment. In contrast, patients with psychoneurosis or psychotic depressions have an undue amount of guilt feelings to which they react with a need for punishment. Often the symptoms fulfill this need. Anxiety symptoms may represent the fear of punishment. These patients have identified in childhood with parents who were too demanding or too strict. Thus too much guilt leads to neurosis or depressions; too little guilt leads to the development of psychopathic personality. In the treatment of psychopathic personalities one of the goals is to "mobilize" the patient's guilt feelings. When this occurs, anxiety symptoms may appear. The fact that this patient has frank symptoms of psychoneurosis makes me believe that the outlook is not so hopeless. To date he illustrates the limitations of certain therapies. Can we go beyond pointing out a correlation between symptoms and situations? The thing to decide on is the next therapeutic move. Can we not do more? More insight? I am not sure if it is possible but it is worth trying. If he would stay, I would keep him until I had gone into the dependency problem. I would attempt insight therapy dealing with his dependency and his reactions to it.

DISPOSITION AND FOLLOW-UP

The patient stayed in the ward about a week longer and the interviews were directed toward the problem of his dependency. The exacerbation of symptoms which had resulted in the laparotomy was reviewed and it was suggested to the patient that the important factor at that time was that the whole load of caring for the family fell upon him. The following interpretations were made: Anxiety symptoms or illness (the ulcer) seemed to appear when he had to make independent decisions or assume responsibilities. (Examples of this reaction were cited from the interview material, as nearly as possible phrased in his own words.) It was pointed out how he had wanted someone to take care of him and had wanted no responsibilities. Actually this state could

be obtained in childhood, and a normal childhood was something he had missed and had always longed for. When his responsibilities weighed upon him, anxiety resulted—the fear that he could not adequately cope with his obligations. One solution to the problem had been sickness (examples were given from the material showing how his ulcer symptoms and some injuries served this purpose.) It was pointed out, also, how his numerous fantasies and worries about disease suggested that if he could develop disease his problem might be solved, i.e., he could then be dependent in a legitimate manner.

The patient did not agree with the interpretations but nevertheless left the hospital much improved. His anxiety was mild and the ulcer symptoms had disappeared. He went back to work and when seen a month later was still feeling well. He has not returned. A year and a half after discharge he reported that he was working regularly and did not feel the need for further treatment.

SUMMARY

A patient with a duodenal ulcer and anxiety attacks was treated by a conventional medical regimen (diet and antacids) and by brief psychotherapy. This case was selected to illustrate important points in the psychiatrist's technic. Essentially what he did was to encourage the patient to talk freely, always with the emphasis upon emotionally charged topics, until the detailed material thus obtained provided a clear correlation between symptoms and repetitively recurring behavior patterns. This correlation was then pointed out to the patient, i.e., "interpreted." It is important to note that the interpretations were not based upon preconceived theories of the psychiatrist but were in fact made only from the material produced by the patient in the interviews.

It is believed that when the relationship between emotion-provoking events and the reactions of the patient are understood, a modification of the symptoms and improve-

ment of personal and reality adjustment may result.

In this case the patient had good insight into the temporal relationship of symptoms and situations. His formula was: "When things go bad my ulcer goes bad." This was true but he had been unaware of the basic conflict which was uncovered in the interviews. On one hand he had an extreme desire for dependency and security and on the other a wish for freedom and no responsibilities. In certain situations in which he could accept his dependent needs he got along without symptoms. Sometimes the conflict was "solved" by illness, either

ulcer or anxiety attacks. The formula might then be expressed: "If I am sick, then I can be dependent legitimately."

A good doctor-patient relationship developed in which the patient who had never had satisfactory relationships with men came to trust and depend upon the therapist. It is possible that a good deal of the success in this case depended upon this relationship. When such a patient finishes treatment and loses the sustaining therapist, one must keep in mind the possibility of a flare-up of symptoms. It may be necessary to continue seeing the patient at infrequent intervals for "supportive" interviews.

Clinico-pathologic Conference

Pneumonia and Empyema^{*}

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, A. M., (B. H. No. 162439), was an eighty year old, unemployed, white male who entered Barnes Hospital on August 15, 1948, complaining of cough, chest pain, chills and fever. The family history revealed that the patient's mother had died at the age of sixty-eight from a "stroke." His father had had known tuberculosis for many years but died at fifty-two from carcinoma of the stomach. One brother had died at the age of sixty-two from cancer of the kidney. During his long lifetime the patient had enjoyed relatively good health until his latter years. He stated that he had had "head colds" every winter and for twenty years he had noted pain in the front of his chest which was unrelated to exertion and was never severe. During a similar period he had had dyspnea on moderate exertion, but at no time had he experienced orthopnea or paroxysmal nocturnal dyspnea. He had had some frequency and dysuria intermittently for a number of years. All of the symptoms listed had progressed only slightly. The patient had worked in a shoe factory until the age of seventy at which time he retired.

Four years before admission to the hospital the patient had an upper respiratory infection following which he developed a cough which persisted. The cough was productive of approximately one-fourth of a cup of grey mucoid sputum daily, but the sputum was never bloody; the cough was most severe in the morning, particularly during the winter. Over the course of the four-year period dyspnea on exertion gradu-

ally increased until it became marked, and for three years the patient had rather persistent ankle edema. Five months before his admission to the hospital he came to the Washington University Clinics because of cough and dyspnea. Examination revealed signs which suggested cardiac decompensation. A film of the chest showed a prominent shadow at the right hilar region. There were also increased markings at the right base which were thought to be compatible with pneumonitis. The patient was referred to the chest clinic. The hilar shadow was thought to be vascular in origin and a diagnosis of emphysema was made. Because of his urinary complaints, he was also referred to the genito-urinary clinic; no significant abnormalities were found. The patient was given medication for relief of his cough and he improved somewhat. While attending the clinic, however, he lost 20 pounds and became noticeably weaker.

Four days before entry the patient fell into the river while fishing and swallowed a considerable amount of cold, muddy water. The two friends who had accompanied him on the fishing trip were elderly and were unable to pull him out of the water; he was thus forced to remain partially immersed for about one hour. The return trip to his home consumed several more hours and by the time the patient arrived he had begun to have chills and to feel feverish. Soon thereafter he noted pain in the left lower chest which was pleuritic in character. His cough increased in severity and sputum became profuse

^{*} From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

and discolored. His symptoms grew worse and the pain spread to involve the entire thorax; it was particularly severe on the left side. One day before admission he coughed up a cupful of thick, brownish sputum. Because of his weakness and chest pain the patient found expectoration very difficult. He was seen by a physician who gave him an unknown amount of penicillin and apparently performed a thoracentesis but no information in regard to the procedure could be obtained.

On admission to the Barnes Hospital the patient's temperature was 37.5°C., pulse 92, respirations 22 and blood pressure 90/50. The patient was a well developed but poorly nourished elderly male in moderate respiratory distress lying flat in bed. He complained of pain in the left chest. The skin was pale. There was edema of the legs, sacrum and scrotum as well as of the lower left chest wall posteriorly. Edema was also noted in the left axillary region which was tender on palpation. The pupils reacted well to light and to accommodation. Examination of the fundi revealed narrowing and tortuosity of the arterioles. The nose and throat appeared essentially normal. The mouth was edentulous. The neck veins were not distended. The trachea was in the midline. Respiratory excursion was unequal, being greater on the right than on the left and there was hyper-resonance to percussion over the right lung. The left side of the chest was dull to percussion from below the level of the fifth rib posteriorly and the second rib anteriorly. Over this area there was a loss of tactile fremitus, voice sounds were diminished and breath sounds were distant and tubular. Rales were heard at the right base. The cardiac borders could not be determined by percussion and the heart sounds were distant. No murmurs were audible. The rhythm was regular. Examination of the abdomen revealed it to be held rather tensely but no organs or masses were felt. The inguinal rings were both large. The prostate was approximately twice normal size but rectal examination was not otherwise remarkable. Aside from absent

knee and ankle jerks the neurologic examination was within normal limits.

Laboratory data were as follows: Blood count: red cells, 3,300,000; hemoglobin, 7 Gm.; white cells, 11,200; differential count: juvenile forms, 10 per cent; stab forms, 36 per cent; segmented forms, 54 per cent. Urinalysis: albumin, negative; sugar, negative; centrifuged sediment, many white cells with numerous clumps. Urine culture: no growth. Stool: guaiac faintly positive. Blood Kahn test: negative. Blood culture: negative. Sputum smear: many cocci in pairs and clusters; sputum culture: *Bacillus proteus* and coliform organisms. Blood chemistry: non-protein nitrogen, 36 mg. per cent; total proteins, 4.8 Gm. per cent; albumin, 2.3 Gm. per cent; globulin, 2.5 Gm. per cent; chlorides, 101 mEq./L.; carbon dioxide combining power, 26.6 mEq./L.; calcium, 8 mg. per cent; phosphorus, 4.7 mg. per cent; alkaline phosphatase, 3 Bodansky units; acid phosphatase, 2 King-Armstrong units; cephalin-cholesterol flocculation test, 2+; thymol turbidity, 2 units; icterus index, 4.5 units. Prothrombin time: 44 per cent of normal. Coagulation time: three and one-half minutes. Bleeding time: one and one-half minutes. Blood indices: mean corpuscular volume, 115 cu. micra; mean corpuscular hemoglobin, 35 gamma gamma; mean corpuscular hemoglobin concentration, 30 per cent. Electrocardiogram: abnormal form of ventricular complex as evidenced by a low upright T wave in lead I and inverted principle components in leads II and III.

Respiratory isolation was instituted and the patient was given large doses of penicillin parenterally. Fluids were forced by mouth. Thoracentesis was performed and 100 cc. of cloudy yellow fluid were removed. Examination of the fluid revealed large numbers of polymorphonuclear leukocytes. On culture *B. proteus* was recovered. No tumor cells were identified on microscopic examination of a cell block section. On the day following entry the patient's red cell count was 2,470,000 with 8 Gm. of hemoglobin. The white cell count was 5,750 with

a marked left shift in the differential count. Another sputum culture was reported as showing beta-hemolytic streptococci and coliform organisms. On the third hospital day a second thoracentesis was performed. Three hundred cc. of cloudy, greenish purulent fluid with a foul odor were obtained and 200 cc. of gas were also removed. The white cell count on the pleural fluid was 5,800 and culture revealed coliform organisms. Eighty thousand units of penicillin and 0.1 Gm. streptomycin were instilled into the pleural space. Following the procedure, the patient developed extreme weakness, cyanosis, gasping respirations and his pulse became thready. His blood pressure fell to 60/30. Large amounts of mucus were aspirated from the pharynx and trachea and oxygen was given by nasal catheter. The patient also received parenteral streptomycin, blood transfusions, caffeine, adrenal cortical extract and desoxycorticosterone acetate. His condition remained essentially unchanged; tracheal suction was repeated as indicated.

Dependent edema increased although the venous pressure was only 110 mm. of water and the neck veins were not distended. During the fourth day the patient was noted to have developed stiffness of the neck and a lumbar puncture was performed. The initial pressure was 300 mm. of water and the final pressure 250 mm. of water. The spinal fluid was entirely negative. During his hospital stay the patient's blood pressure had never risen above 90/50. His temperature rose to a peak of 39.2°C. on the third day and fell gradually until death which occurred later on the fourth hospital day, August 19, 1948.

CLINICAL DISCUSSION

DR. W. BARRY WOOD, JR.: Before we begin our discussion of this case I should like to ask Dr. Grunow to comment on the x-ray films.

DR. OTTO H. GRUNOW: A chest film taken on the day of admission showed that the cardiac silhouette was obscured by fluid which occupied the entire lower half

of the left chest. A lateral view of the chest showed a distinct fluid level superiorly and some areas of decreased density which were suggestive of encapsulated fluid. In the lateral view there was also evidence of pneumonic infiltration in the posterior sulcus.

DR. WOOD: In this case, in contrast to the situation which often obtains, we have a very excellent history. I particularly should like to read part of the present illness as it was described by a senior student who was a clinical clerk on the ward to which this patient was admitted:

"The present illness proper began four days prior to entry when the patient and two friends went fishing in the country. He had had few complaints in the preceding few days and felt quite well. He accidentally stumbled, however, and fell head first into the stream, swallowing quite a lot of the rather muddy cold water. He regained his feet but could not climb back onto the bank. His friends, both elderly, were unable to pull him out and ran for help. Finally after about one hour, he was pulled from the water. Within a few minutes he began to have chilly sensations but no shaking chills. His cough became marked and was productive of a small amount of thick, brown sputum. It began to rain and the three men waited about an hour until the rain stopped before taking the bus back to the town in which they lived. The patient's cough meanwhile became increasingly severe; he felt feverish and had mild shaking chills.

"When he reached home, he was immediately put to bed and an electric heating pad was used for increased warmth. Within six or eight hours his lower left chest began to pain with each respiration and his muscles and joints ached. The cough continued to increase in severity and the sputum became gradually more profuse and browner (? rusty) in color. The chills increased in severity and frequency and the patient felt hot and sweated moderately. His temperature was not taken.

"He spent an extremely restless night because of the chest pain and cough, and

the following day was very weak and anorectic. He noted the onset of constant hiccoughs. His symptoms grew increasingly severe and respiration and cough became more painful because of chest pain. The pains gradually spread to cover both lower chest regions and radiated to both shoulders. Pain was most marked over the left chest. There was no nausea or vomiting and the patient was apparently not irrational at any time. On the third day his symptoms continued unabated and he brought up about one cup of thick brownish sputum which was not foul. He felt extremely weak and found it difficult to cough because of weakness and chest pain. On the morning of the fourth day, he was brought to the Barnes Hospital by ambulance."

I believe that this very graphic and complete description of the present illness quite clearly points to the primary diagnosis but since some of the problems involved are fairly complicated, it might be well to consider briefly each of the four phases of this man's illness. The first phase began four years prior to his entry into the hospital and was characterized by cough, dyspnea and later edema. During the second phase the patient was seen in the clinic and the abnormal finding on the chest film was described for the first time. The third phase followed the patient's falling into the stream and the final phase became apparent only after thoracentesis had been performed in the hospital. If we can interpret the clinical data correctly during each of these four phases, we should reach the correct diagnosis.

Dr. Scott, this patient had complained of cough for four years and had produced rather copious amounts of sputum which had never been bloody; in addition, he had had dyspnea and for three years ankle edema. How would you explain these findings?

DR. VIRGIL C. SCOTT: In a patient of this age we should first consider emphysema.

DR. WOOD: The radiologists seem to substantiate your impression that the patient had emphysema.

DR. SCOTT: Second, there seems to be

evidence of chronic inflammation of the bronchi which took the form of bronchitis, perhaps associated with bronchiectasis.

DR. WOOD: Dr. Flance, do you agree with Dr. Scott's interpretation?

DR. I. JEROME FLANCE: Yes, I would certainly think that this patient had chronic bronchitis and probably bronchiectasis.

DR. WOOD: If it is assumed that this patient had both bronchitis and bronchiectasis, I should like to ask Dr. Goldman if he is disturbed by the absence of clubbing.

DR. ALFRED GOLDMAN: The absence of clubbing is somewhat disturbing and, likewise, the fact that the patient did not have purulent sputum does not seem entirely consistent with the diagnosis of bronchiectasis.

DR. WOOD: According to the history, the patient's sputum was not purulent. Dr. Rouse, do you have any further information regarding this point?

DR. ERNEST T. ROUSE: At no time were we able to elicit a history of purulent sputum.

DR. GOLDMAN: In regard to the problem of bronchitis and bronchiectasis it should be emphasized that it is often very difficult to be certain whether the transition from bronchitis to bronchiectasis has occurred.

DR. ROBERT A. MOORE: I would agree with Dr. Goldman in that regard. There is no distinct line pathologically between bronchitis and bronchiectasis.

DR. WOOD: Dr. Goldman, what is your view in regard to the hilar mass which was described on the chest film taken when the patient was seen in the clinic?

DR. GOLDMAN: I believe that the shadow represents a pulmonary vessel rather than a tumor. I do not believe that it is suggestive of bronchogenic carcinoma.

DR. WOOD: Do you not think, however, that bronchogenic carcinoma deserves consideration in view of the patient's weight loss and anemia? Dr. Grunow, what is your opinion?

DR. GRUNOW: It is often difficult on roentgen examination to differentiate a mass due to a large vessel from that due to a tumor. I believe, however, as does

Dr. Goldman that in this particular case the shadow represents a vascular marking. Further, the fact that the hilar mass was on the right side and the patient's subsequent pulmonary lesion developed on the left side would seem to me to be against the diagnosis of tumor.

DR. WOOD: Let us now consider the third phase of this man's illness which began after he fell into the river. As you recall he developed chills, fever, chest pain and a cough productive of brown sputum.

Dr. Harford, what lesion is usually associated with such a history?

DR. CARL G. HARFORD: Pneumonia.

DR. WOOD: The story certainly suggests acute bacterial pneumonia. Can you tell us, Dr. Harford, something of the effects of immersion on pulmonary infection in general? What happens when a patient takes in a large amount of water as this patient apparently did?

DR. HARFORD: I have been interested in the effects of fluid on the susceptibility of the lung to infection by the pneumococcus. Very likely when this man fell into the water and "swallowed" a large amount some of it gained access to his trachea and bronchi. Most of the organisms which cause pneumonia, particularly the gram-positive cocci, are non-motile. Their transport, therefore, in the lung depends on the presence of fluid. The importance of edematous fluid in causing the spread of experimental pneumococcal pneumonia is well established. It is by way of edematous fluid that the pneumococci are carried not only from one bronchus to another but from alveolus to alveolus. This patient, who had chronic bronchitis, certainly harbored numerous bacteria in his pulmonary tree and these were undoubtedly spread to a number of areas in his lungs by the aspirated water. At some of these sites the organisms multiplied and widespread infection resulted.

DR. WOOD: Another important point in the history is that this patient stood in the river for an hour in the cold water and then stood out in the rain for another hour before he was taken to his home. Dr. Smith, what

is the effect of chilling in such a situation as this? Is external chilling of importance in the pathogenesis of acute pulmonary infection?

DR. RALPH O. SMITH: It has been shown in experimental animals that chilling increases susceptibility to pneumonia. Certainly patients frequently give a history of having been chilled prior to the onset of respiratory infection. The phenomenon is probably associated with vasoconstriction or with the effect that chilling has on the mucous membranes of the bronchi *per se*.

DR. WOOD: Nungester at the University of Michigan studied the effect of chilling on experimental pulmonary infection in rats. He introduced pathogenic organisms into the upper respiratory tract of animals and then exposed them to low temperatures. The incidence of pneumonia in animals so chilled was significantly higher than in animals who had not been subjected to low temperature. Dr. Nungester presented evidence that chilling slows the epiglottis reflex which normally prevents the infected mucus of the nasopharynx from entering the trachea.

DR. HARFORD: Many years ago Dr. Goldman carried out some interesting experiments on the influence of chilling in human beings.

DR. WOOD: Yes, Dr. Goldman, in conjunction with Dr. Samuel Grant and Dr. Stuart Mudd, who is now Professor of Bacteriology at the University of Pennsylvania, undertook these experiments while they were medical students in this School. Dr. Goldman, would you tell us about this work.

DR. GOLDMAN: We were told by one of our instructors in pathology that chilling of the body resulted in congestion of all the organs. We were skeptical regarding his statement and attempted to examine its validity. We first determined the temperatures of mucous membranes in the nose, throat, pharynx and larynx with a thermocouple. After these control observations we entered an icebox and chilled ourselves as thoroughly as possible. Following chilling,

we found that ischemia rather than congestion developed in the upper respiratory tract and we usually developed sinusitis, laryngitis, pneumonitis or pleurisy within a few days after exposure. We also studied the bacterial flora of the mucous membranes and found that streptococci, for example, would persist after chilling longer than many of the other common inhabitants of the respiratory tract. We concluded that ischemia lowered the resistance of the mucous membranes and allowed pathogenic bacteria to flourish.

DR. WOOD: It seems quite clear then that this patient had pneumonia. The final phase of his illness began after he was admitted to the hospital and it was discovered that he had early empyema. The fluid removed from his chest was thin at the time of the first thoracentesis but subsequently became very thick and *B. proteus* and coliform organisms were cultured from the fluid. Furthermore, a rather large amount of air was withdrawn at the time of the second thoracentesis. Dr. Goldman, would you comment on the development of the empyema.

DR. GOLDMAN: It seems likely that this patient had a mixed pulmonary infection from the beginning and that empyema developed in one of two ways: either by direct extension of the infection to the pleura such as is common in pneumococcal pneumonia or by abscess formation and subsequent rupture of the abscess directly into the pleural cavity with the development of a fistula. In view of the fact that the patient brought up a cupful of brownish sputum very early in the course of his acute illness it would seem likely that the pneumonic process was a necrotizing one and probably extended into the pleural cavity directly. The presence of so much air suggests a bronchopleural fistula.

DR. WOOD: The organisms that were grown from the empyema fluid, Dr. Harford, were not those commonly identified as etiologic factors in pneumonia. How do you explain their presence in the pleural cavity?

DR. HARFORD: *B. proteus* is a common contaminant. Despite rigid technical precautions the possibility of a contaminated culture must be considered.

DR. WOOD: *Proteus* was also recovered in the sputum and it would seem unlikely, would it not, that both cultures could have been contaminated? Furthermore, the fluid was foul, as it occurs in empyema, due to coliform organisms. Dr. Flance, would you be inclined to consider the possibility of suppuration close to the pleura with subsequent rupture of an abscess as the cause of the empyema?

DR. FLANCE: That explanation seems to me to be the most logical. It is conceivable that the patient originally had a very small opening into the pleural space which subsequently was widened.

DR. WOOD: Also an abscess may rupture into the pleural space and the defect close promptly. In such instances empyema without a demonstrable fistula results.

DR. WILLIAM DAILY: I should like to suggest that this patient had arteriosclerotic heart disease with congestive failure. A rather chronic cough, edema and the subsequent finding of pleural effusion are all consistent with this suggestion.

DR. WOOD: I was just about to ask Dr. John Smith whether he thought this patient had significant coronary artery disease and whether at any time he had cardiac failure.

DR. JOHN R. SMITH: Certainly this patient may have had sclerotic coronary arteries but I did not think that his early edema was due to cardiac failure. Patients in this age group often exhibit some ankle edema after prolonged standing. It is conceivable that following development of the severe infection cardiac failure ensued as a complication.

DR. WOOD: Why was edema noted over the site of the thoracic lesion?

DR. J. R. SMITH: The patient probably lay on that side in order to relieve his chest pain and the edema may have developed because of the dependence of that region.

DR. WOOD: Patients with pneumonia usually lie on their affected side and edema

is not uncommonly localized because of position.

Dr. HENRY A. SCHROEDER: An alternate suggestion in regard to terminal edema is that it was of renal origin. The patient's blood pressure was low and remained low, and it is conceivable that there was enough decrease in renal blood flow to give rise to edema.

Dr. WOOD: There are two other points which we shall not have time to discuss adequately, but I think that we should mention them in passing: First, the patient had a mean corpuscular volume of 115. Dr. Moore, would you comment on this finding?

Dr. CARL V. MOORE: I see no apparent reason for that result.

Dr. WOOD: Further, the patient's blood calcium was 8 mg. per cent. What about that, Dr. Wade?

Dr. LEO J. WADE: The phosphorus was slightly elevated although certainly not enough to explain the low calcium.

Dr. WOOD: In summary then, we believe that at postmortem examination the findings in this patient will include emphysema, chronic bronchitis, probably with bronchiectasis, acute pneumonia and empyema, possibly as a result of rupture directly into the pleural cavity of an area of pulmonary suppuration. Furthermore, there may be a significant degree of coronary sclerosis and, although not likely, a bronchogenic carcinoma may possibly be present.

Clinical Diagnosis: Acute bacterial pneumonia with empyema (? following rupture of abscess); emphysema; chronic bronchitis; bronchiectasis; ? coronary artery sclerosis; ? bronchogenic carcinoma.

PATHOLOGIC DISCUSSION

Dr. ELLIS J. VAN SLYCK: At autopsy the body was that of a well developed, poorly nourished, elderly white male. There was moderate pitting edema of the ankles, legs, thighs and scrotum.

Upon opening the thorax 400 cc. of thin, blood-tinged fluid were seen to be present

in the right pleural cavity. The left pleural space was the site of a loculated empyema cavity; a thick fibrinous exudate covered the left lung and divided the cavity into several pockets, from which a total of 700 cc. of thick, green, foul-smelling pus were evacuated.

In the lateral aspect of the left lower lobe just beneath the pleura there was a lesion, roughly 5 cm. in diameter, which consisted of black, semisolid, necrotic material which communicated with one of the larger empyema pockets through the perforated visceral pleura. Surrounding this involved area the lung parenchyma was firm, and blood-tinged edematous fluid exuded from the cut surface. Two firm, grey-yellow raised nodules of lung tissue, about 3 cm. in diameter, were seen superimposed on the congested and edematous parenchyma of the left lower lobe. In this same region numerous small thrombi were present in the tertiary branches of the pulmonary artery. Other changes in the lungs were (1) white, firm, stellate scars at both apices; (2) 1 mm. calcified nodules in the parenchyma of the right upper lobe; (3) a calcified nodule, measuring 1 cm. in diameter in the upper portion of the right lower lobe; (4) generalized slight emphysema of the senile type. The mediastinal lymph nodes were moderately enlarged and cut with increased resistance.

The pericardial sac contained 10 cc. of clear yellow fluid. Scanty fibrinous exudate was present on the epicardial surface; it could be removed with ease. The heart weighed 320 Gm., and the outstanding pathologic lesion was found in the coronary arteries where generalized thickening of the walls and narrowing of the lumina was widespread. In the left anterior descending branch a calcified plaque or thrombus, about 1.5 cm. in length, was seen to occlude the lumen completely about 1 cm. from the ostium. The right coronary artery was hypoplastic and failed to establish its normal anastomosis with the circumflex branch of the left coronary. The endocardium of the left ventricle overlying the

septum contained an area, 2 cm. in diameter, which was white and thickened. Patchy streaks of fibrosis were seen in the musculature of the septum. Other findings referable to the heart were moderate sclerotic changes in the aorta, aortic and mitral valves and a duplication of a cusp of the pulmonary valve.

The peritoneal cavity contained 100 cc. of clear yellow fluid. The stomach was remarkable in that the mid-point of the lesser curvature, a polypoid, fungating mass about 10 cm. in diameter, was noted. It was soft, multilobulated, greyish-green in color and on its cut surface several areas of hemorrhage and liquefaction were seen. Extension of the tumor in the subserosal lymphatics was evidenced by the raised white streaks which were visible through the serosa. A large mass of matted lymph nodes, 0.8 by 3 by 3 cm., surrounded the body of the pancreas and included the lesser omentum. When these nodes were sectioned, tan colored, semisolid material oozed forth in some regions; other nodes showed complete replacement of lymphoid tissue by soft white tissue which appeared to be malignant.

Around the abdominal aorta of the level of the renal arteries there was another large conglomerate group of nodes which also appeared to be the site of metastatic growth. The renal vessels were neither occluded nor invaded by metastatic tissue. The liver was likewise free from metastases.

DR. R. A. MOORE: On the basis of the gross examination it is apparent that the pathologic changes fall into three categories, namely, pulmonary, cardiovascular and gastrointestinal. As far as the pulmonary lesions are concerned the gross appearance is certainly that of pneumonia of the necrotizing variety associated with the formation of an abscess in the periphery of the lung and subsequent rupture into the pleural cavity with formation of empyema. Loculation of the empyema cavity was apparent. In regard to the coronary disease there was moderately advanced arteriosclerosis of the major vessels. The heart

which weighed 320 Gm. was probably not grossly enlarged, but there was total occlusion of the descending left coronary artery with an old infarct in the septum. Associated evidence of cardiac disease was the finding of 400 cc. of fluid in the right pleural cavity, 100 cc. in the peritoneal cavity, some edema of the lower extremities and chronic passive congestion of some of the viscera. All of these observations indicate that this patient had some element of cardiac failure. A culture of the fluid in the right pleural cavity remained sterile and thus was not the result of the bacterial infection which affected the left lung and pleural space. Arteriolar sclerosis of the kidneys, that is, nephrosclerosis—was present to a moderate extent.

The lesion in the stomach was identified grossly as a carcinoma of the polypoid type; there were metastases to all of the regional lymph nodes but none to the lungs or liver.

One problem in connection with the infection in the lung is presented. There were thrombi in the tertiary branches of the pulmonary arteries in the involved area, and the possibility that the process represented an infected infarct or an infarct with surrounding pneumonia and subsequent liquefaction and abscess formation must be considered. Grossly, all of the evidence pointed to primary pneumonia, but gross examination *per se* is not sufficient to enable us to exclude occlusion of vessels as a factor in the development of the lesion.

If we turn to the microscopic findings, Figure 1 is a characteristic section of the lung in the region of the abscess. There is total necrosis of pulmonary tissue. The pneumonia is characterized by the presence of a moderate to large amount of fibrin and cells, many of which have undergone karyorrhexis scattered throughout the pulmonary alveoli. The next section (Fig. 2) is a higher power view of the same area and the character of the cells may be seen. There are both mononuclear and polymorphonuclear leukocytes, many of which are undergoing necrosis. This lesion must be considered as an example of a necrotizing

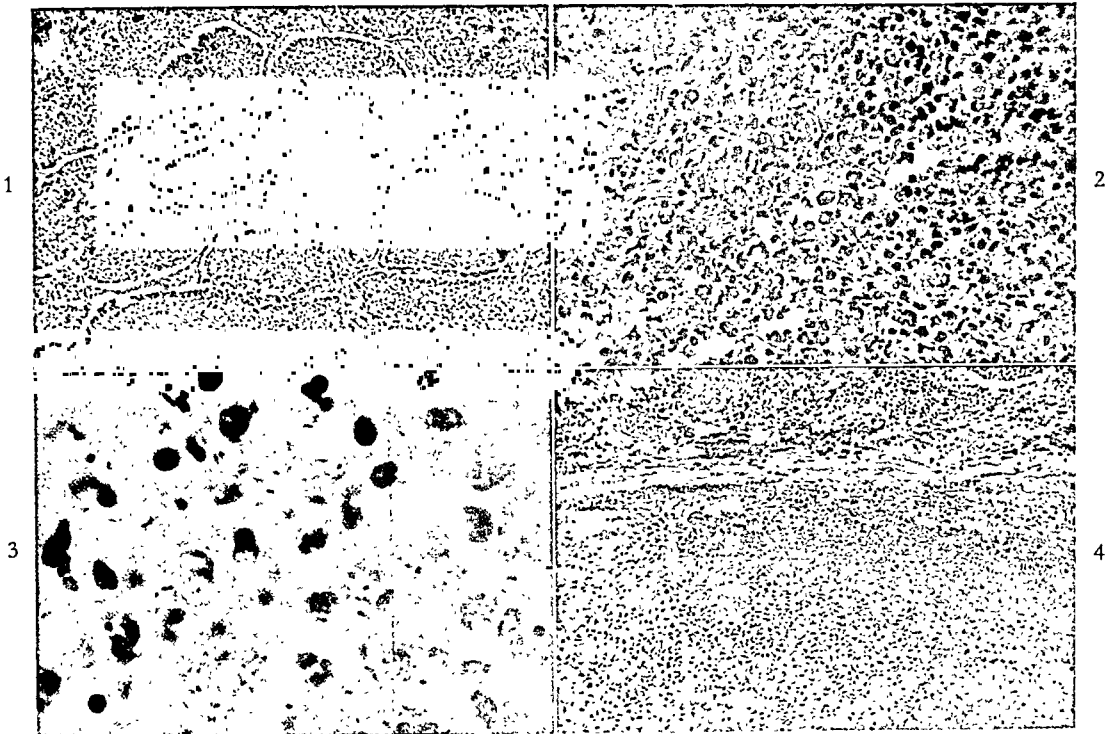


FIG. 1. Section of the lung in the area of necrotizing pneumonia.

FIG. 2. Higher power view of the lesion showing the cellular exudate.

FIG. 3. Oil immersion photomicrograph of a section stained for bacteria; both cocci and bacilli are present.

FIG. 4. Section showing a thrombus in one of the pulmonary arteries.

inflammatory process. In at least one area the alveolar wall has been involved by necrosis and an abscess has been produced. In Figure 3 a photomicrograph of bacteria is shown; in the lesion both gram-positive cocci and gram-negative bacilli are present, some of which have been phagocytized while others are free in the exudate. No culture was made from the lung; a culture of the empyema fluid was reported as yielding hemolytic staphylococcus aureus, a few colonies of a non-specific klebsiella, *Pseudomonas aeruginosa*, a few *Aerobacter aerogenes*, alpha hemolytic streptococci and a few diphtheroids. In attempting to evaluate the bacteriologic findings and to determine the organism or organisms responsible for the pneumonia, the most likely conclusion is that the hemolytic staphylococci plus one of the gram-negative bacilli were probably of major importance.

Figure 4 is a section of one of the pulmonary artery thrombi. The vessel wall may be seen with surrounding lung tissue above

and the thrombus below. Although there is exudate in the alveoli, there is neither an inflammatory reaction within the thrombus nor an increase in cells. Likewise, there is no inflammatory reaction in the vessel wall. I think, therefore, that when one considers the gross and the microscopic findings, he may reject the postulate that this lesion is an example of an abscess resulting from an infarct and instead may accept it as pneumonia which has progressed to necrosis and extension through the pleura. The next section (Fig. 5) bears on the duration of the disease in relation to the diagnoses of bronchitis and bronchiectasis. Although the pleura itself is not thickened, there is a fibrinous exudate on its surface without adhesions and without organization. Thus, the pleurisy is of very recent origin. We were unable to identify dilated bronchi at the time of autopsy; however, I thoroughly agree with Dr. Goldman that the change in a bronchus from the normal to the bronchiectatic state is a gradual one and

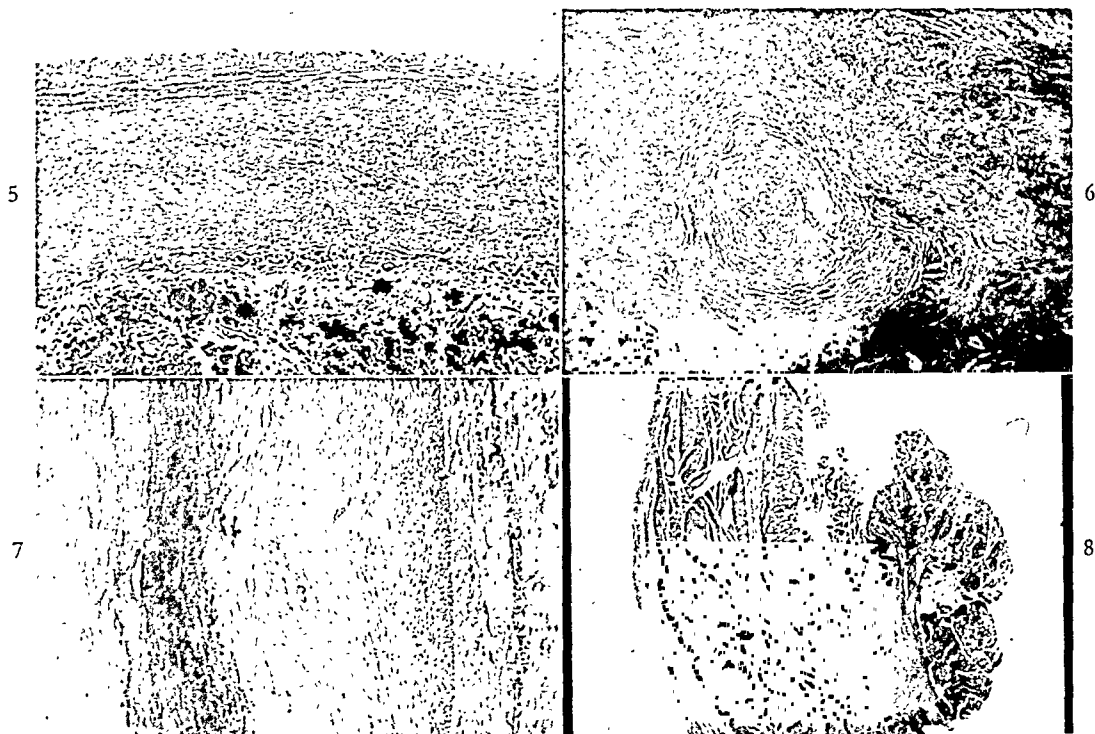


FIG. 5. Section of the pleural wall showing unorganized fibrinous exudate.

FIG. 6. A silicotic tracheobronchial lymph node.

FIG. 7. Section of the anterior descending branch of the left coronary artery showing an arteriosclerotic plaque which obliterates the lumen.

FIG. 8. Low power view of the polypoid carcinoma of the stomach.

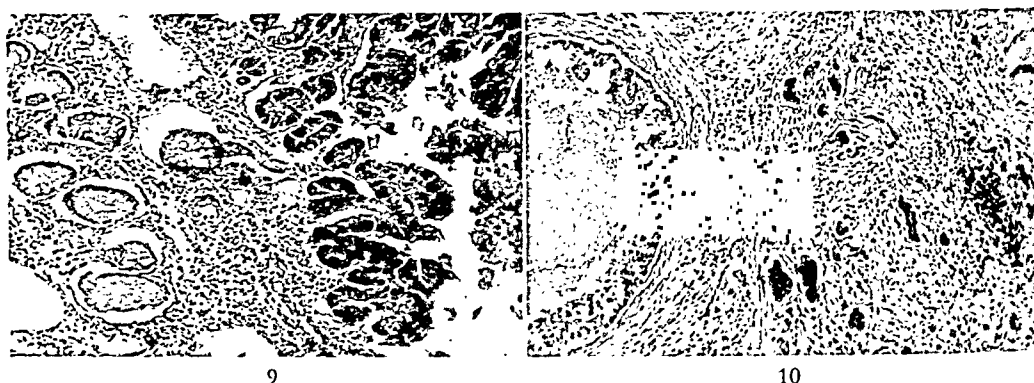


FIG. 9. A higher power view showing the junction of normal and carcinomatous glands in the stomach wall.

FIG. 10. Metastatic carcinoma in a periaortic lymph node.

there is a period during the change when the pathologist is unable to make a definitive diagnosis. The explanation of the patient's four-year history of cough is not apparent to me. In the tracheobronchial lymph nodes (Fig. 6) and to a limited extent in the lungs there are typical silicotic nodules. Looking at these sections, without regard for the history, I would not be impressed with the amount of anthra-

cosilicosis but conceivably it may have played a part in his chronic cough.

Figure 7 is a section of the anterior descending branch of the left coronary artery showing complete or almost complete obliteration of the lumen by an arteriosclerotic plaque containing calcium.

Figure 8 is from the stomach at the edge of the polypoid carcinoma which Dr. Van Slyck described. The transition from normal

mucosa to carcinoma is apparent. The next section (Fig. 9) is a higher power view from the junction of normal and carcinomatous glands. In Figure 10 the periaortic lymph nodes with metastatic carcinoma are seen.

In summary then, Dr. Wood, this man had a recent necrotizing pneumonia with abscess and empyema and pulmonary artery thrombi secondary to the inflammatory process. He also had some cardiac failure, probably on the basis of severe arteriosclerosis of the coronary arteries and an old infarct; finally, there was carcinoma of the stomach with lymph node metastases which probably accounted for the weight loss and anemia, the cause of which was not totally clear clinically.

Dr. Wood: This is a most instructive case for it illustrates that carcinoma of the stomach can be completely silent. Dr. Carl Moore has just pointed out to me two leads in the laboratory data to which we should have paid attention: First, there was more anemia than could be accounted for

by the diagnoses which we made and in one smear there was a suggestion of hypochromia. Later data in regard to the hypochromia were, however, conflicting. Second, one of the stool examinations was positive for occult blood.

Final Anatomic Diagnoses: Necrotizing bronchopneumonia in the lower lobe of the left lung with liquefaction and rupture into the pleural cavity; organizing thrombi in the tertiary branches of the pulmonary artery to the lower lobe of the left lung adjacent to the pneumonia; loculated empyema, left (700 cc.); arteriosclerosis of the coronary arteries, advanced in the left descending coronary artery with occlusion, and of the left circumflex and right coronary arteries, moderate; healed infarct in the anterior myocardial septum; polypoid carcinoma of the lesser curvature of the stomach; metastatic carcinoma in the lymphatics of the serosa of the stomach and the lesser omental, peripancreatic and periaortic lymph nodes about the renal arteries.

Special Feature

Western Society for Clinical Research

SECOND ANNUAL MEETING HELD IN LOS ANGELES, OCTOBER 22 AND 23, 1948

NEUROHUMORAL CONTROL OF HYPOPHYSIAL FUNCTIONS. *Harry B. Friedgood, M.D., Los Angeles, California.* (From the University of California.)

Parenteral administration of the adrenergic substance, neosynephrine, induced pseudo-pregnancy in 50 per cent of thirty-eight rats. This gonadotropic reaction of the rat's adeno-hypophysis was elicited also by electrical excitation of the cervix uteri in 73 per cent of sixty-two control experiments, in 84 per cent of thirty-two experiments after bilateral transection of the cervical sympathetic trunks and in 47 per cent of eighty-four experiments after bilateral superior cervical sympathetic ganglionectomy. These observations, in addition to data derived from previous experiments, constitute evidence for the existence of a neurohumoral adrenergic mechanism which controls the gonadotropic activity of the rat's adeno-hypophysis. Other evidence, stemming mainly from well established anatomic studies of the hypothalamic nuclei and of the angio-architecture of the hypothalamo-hypophysial area, suggests that the hypophysis cerebri is under dual neurohumoral control, viz., an adrenergic element regulates the function of the pars distalis of the adeno-hypophysis, and a cholinergic effect is exercised over the adeno-hypophysis and neurohypophysis. It is postulated that these adrenergic and cholinergic agents are secreted by the hypothalamus, neurohypophysis and proximal portions of the adeno-hypophysis (e.g., pars tuberalis) from whence they are carried via the hypophysial portal circulation to the pars distalis.

The foregoing considerations account satisfactorily on a neuro-anatomic and neurophysiologic basis for those endocrine disorders which are known to be associated with and apparently precipitated by emotional conflicts.

IS THERE A PULMONARY FACTOR IN THE PRODUCTION OF CYANOSIS IN CONGENITAL HEART DISEASE? *Arthur Selzer, M.D., San Francisco, California.* (From Stanford University.)

Blalock and Taussig and other authors have recently emphasized the importance of inadequate circulation or inadequate blood supply to

the lungs in the production of chronic cyanosis in congenital heart disease. Physiologically, the important question in the pathogenesis of chronic cyanosis is whether low arterial oxygen saturation is due to admixture of venous blood shunted from the right side of the heart into the arterial system or due to defective oxygenation of blood in the lungs.

This problem is approached from the pathologic standpoint, by an analysis of over 150 autopsied cases of congenital heart disease. In almost all cases clinically associated with cyanosis findings suggested a right-to-left intracardiac blood shunt. The most convincing evidence of the role which a venoarterial shunt plays in the pathogenesis of cyanosis is an analysis of cases of pulmonary stenosis with closed interventricular septum. It is shown that cyanosis is present if a patent foramen ovale offers a path for intracardiac shunt and is absent if the foramen is closed. The degree of cyanosis is related to the size of the foramen.

No direct or indirect evidence has been found for defective or incomplete pulmonary oxygenation. The beneficial effect of the Blalock-Taussig operation is best explained on the basis of recirculation of poorly oxygenated arterial blood through the lungs.

It is concluded that venous arterial blood shunt is the principal cause of chronic cyanosis in congenital heart disease. There is no known pulmonary factor in its production and the terminology of inadequate blood supply to the lungs is misleading and should be abandoned.

THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN HUMAN ARTERIAL HYPERTENSION. CARDIAC OUTPUT STUDIES IN DIFFERENTIAL SPINAL BLOCK. *Sidney S. Sobin, M.D., Los Angeles, California.*

Of the cardiovascular factors concerned in regulation of blood pressure the abnormality in human hypertension is believed to be an increased total peripheral resistance (TPR). Since TPR cannot be measured directly and is related to arterial pressure and cardiac output as defined by the equation $R = \frac{P_m \times 1332}{C.O.}$ dynes cm.⁻⁵ sec., measurement of these latter

two parameters provides TPR. Cardiac output was determined by the ballistocardiograph (Nickerson) and blood pressure by sphygmomanometer in eight hypertensive and three normotensive individuals under basal conditions and in various stages of sympathectomy produced by differential spinal block. Blood pressure fell in hypertensive patients but remained constant in normotensives despite similar degrees of sympathetic block. Concomitant with the fall in blood pressure in the hypertensives there was a striking increase in cardiac output and a marked fall in peripheral resistance. The course of events following the initial fall in blood pressure with the increase in cardiac output and decrease in peripheral resistance varied somewhat in different patients.

It is suggested that the increased cardiac output resulted from arteriolar dilatation and increased vis-a-tergo of venous return and that this may indicate tonic activity of the sympathetic nervous system in maintenance of the elevated blood pressure in human hypertension.

EFFECT OF ARTERIAL INSUFFICIENCY ON THE CIRCULATION RATE AND THE VOLUME INCREASE RATE OF THE EXTREMITY.
Travis Winsor, M.D., Los Angeles, California. (From the Nash Cardiovascular Foundation of the Hospital of the Good Samaritan.)

Studies on normal individuals and patients with vascular disease have shown definite differences in the time required for an increase to appear in the volume of the digit after partial emptying of blood from the peripheral vascular tree. An awareness of magnitudes of these differences occasionally gives insight into the extent and type of vascular diseases which may be present. The variations and types of response in individuals with different types of vascular disease indicate that this measurement may have merit under certain circumstances. It is the purpose of this report to describe a method for determining an extremity circulation time, an extremity circulation rate and a volume increase rate employing the plethysmographic technic, to present normal values for the extremity circulation time, extremity circulation rate and digital volume increase rate and to show deviations from the normal among patients with various degrees of arterial insufficiency.

From the procedures outlined retarded circulation rates and volume increase rates ordinarily indicate organic disease, whereas normal circu-

lation rates and retarded volume increase rates indicate organic disease or vasospasm. It is believed that these measurements may aid in gaining insight into the type and extent of vascular disease which may be present. Further study is necessary to evaluate the influence of edema, sympatholytic procedures, hypertension and alterations in tissue distensibility.

STUDY OF THE RATE OF DISAPPEARANCE OF A DIGITALIS GLYCOSIDE (LANATOSIDE C) FROM THE BLOOD OF MAN. *Meyer Friedman, M.D. and (by invitation) Rene Bine, M.D., San Francisco, California.* (From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital.)

By means of the embryonic duck heart preparation it was found possible for the first time to determine the concentration of digitalis glycoside (Lanatoside C) in the sera of patients at various intervals of time after they had received the glycoside by vein.

It was found that the average concentration of glycoside in the ten patients studied was 0.25 microgram per cc. of serum immediately after the intravenous injection of 1.6 mg. of Lanatoside C. Seven and one-half minutes after injection the average concentration was 0.10 microgram per cc. of serum. At the end of fifteen minutes no glycoside could be detected in two of the ten patients and the average concentration in the remaining eight patients was 0.07 microgram per cc. of serum. At the end of thirty minutes glycoside (0.05 microgram per cc.) was detected in only one of the ten patients. No glycoside could be detected in any patient one hour after its injection.

These results indicate that after intravenous injection of a digitalizing dose of the particular glycoside employed (Lanatoside C) a very rapid disappearance of the drug from the blood stream occurs.

A QUANTITATIVE STUDY OF ATHEROSCLEROSIS. *Alvin J. Cox, M.D., San Francisco, California.* (From Stanford University.)

Dehydration and extraction of 220 human aortas removed at autopsy yielded amounts of fatty material which were related to the age and sex of the corresponding patients. Comparison of different groups of the aortas shows more aortic lipid from those with hypertension and diabetes than from others without these conditions. There is little evidence of a significant effect of diet upon the amount of aortic lipid

although poorly nourished and alcoholic individuals had aortas containing slightly less lipid than the controls.

THE ROLE OF LIPOID METABOLISM IN PRODUCTION OF CORONARY ARTERIOSCLEROSIS AND ATHEROSCLEROSIS. *Lester M. Morrison, M.D., Albert L. Chaney, Ph.D., (by invitation) Lillian Hall, M.D. and (by invitation) William Gonzalez, M.D., Los Angeles, California.* (From the Los Angeles County General Hospital and the Department of Internal Medicine, Medical School of the College of Medical Evangelists.)

The effect of choline on the prevention of experimental cholesterol atherosclerosis: The oral feeding of 0.5 Gm. choline chloride daily, together with 0.5 Gm. cholesterol to twenty-nine, three-month old rabbits prevented atherosclerosis in 55 per cent of the animals at the expiration of the ninety-second-day experimental period. The oral feeding of 1.0 Gm. choline chloride daily together with 0.5 Gm. cholesterol to thirty-two three-month old rabbits prevented atherosclerosis in 78 per cent at the expiration of the ninety-second-day experimental period.

Absorption of aortic atherosclerosis by choline feeding: Choline caused re-absorption of aortic atherosclerosis in the majority of rabbits with lesions produced by cholesterol feeding.

Effect of blood cholesterol disorders on the coronary arteries and aorta: A series of 600 patients with diseases characterized by hypercholesterolemia and hypocholesterolemia during life was studied in relationship to coronary artery arteriosclerosis and aortic atherosclerosis as found at autopsy. These patients were compared to "controls" or patients in a series of deaths from sudden, acute illness (medical or surgical) and to a series of patients who died of chronic illnesses other than those of the other groups described. Patients who died of chronic diabetes mellitus, a disease characterized by hypercholesterolemia, showed a marked increase in coronary arteriosclerosis and aortic atherosclerosis as compared to a series of control patients who died of an acute illness and a series of control patients who died of chronic illnesses and a series of deaths from cancerous illnesses. Patients who died of chronic thyrotoxicosis, a disease characterized by hypocholesterolemia, showed a marked decrease in incidence of

coronary arteriosclerosis and aortic atherosclerosis as compared to the control series and all other groups described herein.

Cholesterol content of the coronary arteries and blood in acute coronary thrombosis: The average cholesterol content of the coronary arteries in a series of patients who died from an acute coronary artery thrombosis was analyzed biochemically and found to be four times as great as the average cholesterol content of the coronary arteries in a comparable group of control patients. Hypercholesterolemia was found (average value) in the group of patients who died of acute coronary artery thrombosis as compared to a normal blood cholesterol average in the comparable control group.

Changes in the blood cholesterol levels following one year of choline therapy in patients with acute coronary thrombosis: In summary, in a series of thirty-two normal subjects the constancy of blood serum cholesterol levels was re-affirmed over prolonged test periods using a modification of the Sperry-Schoenheimer serum cholesterol procedure. Wide variations in serum cholesterol values were found in a group of thirty-one patients with miscellaneous diseases. Marked fluctuations in serum cholesterol values were observed in a series of fifty patients who had recently experienced a coronary artery thrombosis. Analogous wide fluctuations in serum cholesterol values were found in a series of forty-eight patients who had recently experienced a coronary artery thrombosis and ingested 6 Gm. of choline daily. These fluctuations rendered it impracticable to determine whether choline effected a reduction or increase in serum cholesterol levels. It is suggested that variations in serum cholesterol exceeding 15 per cent when determined by the Sperry-Schoenheimer procedure or a proven modification thereof in an individual presumed to be normal may possibly indicate a systemic disorder or latent illness.

QUANTITATIVE ESTIMATION OF ALBUMIN, GAMMA GLOBULIN AND BETA-1 GLOBULIN IN HUMAN BODY FLUIDS BY IMMUNOLOGIC TECHNIQS. *B. V. Jager, M.D. and (by invitation) Margaret Nickerson, Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

Antisera to highly purified serum albumin and to human serum gamma globulin and to a beta-1 globulin (Fraction IV-7-4) have been

prepared in rabbits. Employing quantitative precipitin technic, the amounts of proteins reacting to these antisera have been determined, using whole human serum and spinal fluid as antigens. For human serum antigens the immunologically estimated serum albumin is in close agreement with the electrophoretic estimation. For human serum gamma globulin the immunologic values are far in excess of electrophoretic estimations of gamma globulin. The reactive antigen in human serum to iv-7-4 antiserum comprised approximately 3 per cent of the total serum protein in blood from three normal subjects. In spinal fluids the values for serum albumin and serum gamma globulin were in agreement with the values obtained by Kabat and co-workers (1948). Certain theoretical and practical limitations of the quantitative precipitin technic are considered.

ELECTROPHORETIC STUDIES OF SERUM MUCOPROTEINS. *John W. Mehl, M.D., Jane Humphrey, (by invitation) Florence Golden, (by invitation) and Richard J. Winzler, Los Angeles, California.* (From the Los Angeles County General Hospital and the Department of Bio-chemistry and Nutrition, University of Southern California School of Medicine.)

Previous studies have shown that an increased amount of "proteose" appears in the plasma or serum of patients with neoplastic and infectious diseases. Previous investigations of this material have shown that it is a mucoprotein.

Electrophoretic studies of this mucoprotein isolated from normal human plasma by chemical procedures show that it is present in the α_1 -globulin fraction at pH 8.4. Studies of the mobility as a function of pH have shown that it is heterogeneous but that all of the components have an isoelectric point below that of the other normal serum proteins. These studies indicated that a pH of 4.5 would be most advantageous for the demonstration of these mucoproteins by direct electrophoretic studies of serum since at this pH all other normal serum proteins would be positively charged.

The electrophoretic study of normal serum has shown that there are two components which are still negatively charged at pH 4.5. These two components are increased, but not always in the same proportions, in conditions in which the mucoprotein determined by chemical means is increased. One of these components has been

isolated by electrophoresis from pathologic serum and found to have essentially the same chemical properties as the material prepared by precipitation from normal serum. Both of the components which are elevated in pathologic sera may be increased by adding the mucoprotein precipitated from normal serum.

EFFECT OF PARENTERAL BOVINE ALBUMIN INJECTIONS ON EXCRETION OF HEMOGLOBIN IN THE RAT. *Richard W. Lippman, M.D. (introduced by David Ryland, M.D.), Los Angeles, California.* (From the Institute for Medical Research, Cedars of Lebanon Hospital.)

Addis and his associates have shown that massive proteinuria may be induced in rats by the parenteral injection of bovine albumin and other proteins. This study was made to analyze the proteinuria with respect to the factors of filtration and re-absorption through the use of hemoglobin as an indicator protein.

Animals received an intravenous injection of hemoglobin at the height of proteinuria produced by the injection of bovine albumin intraperitoneally. Serum concentrations of hemoglobin and the excretion rate of hemoglobin were measured. Control animals received intraperitoneal injections of 0.85 per cent sodium chloride solution. The animals who received albumin excreted hemoglobin at double the rate of the controls. In addition the serum concentration threshold for hemoglobinuria was reduced from 75 mg. per 100 cc. to less than 25 mg. per 100 cc. These results were interpreted to indicate both diminished tubular re-absorption of protein and increased glomerular permeability to protein in experimental animals.

METABOLISM OF ENDOGENOUS AND EXOGENOUS ANDROGENS BY PATIENTS WITH LIVER DISEASE. *Laurance W. Kinsell, M.D. and Maxine E. Hutchin (by invitation), Sheldon Margen, M.D., San Francisco and Oakland, California.* (From the Division of Medicine, University of California Medical School and Department of Medicine, U. S. Naval Hospital.)

Reports by a number of clinicians and investigators indicate that the liver normally plays a major role in the metabolism of steroid hormones. It has also been suggested that certain

endocrine abnormalities noted in some patients with acute and chronic liver damage are referable to malmetabolism of endogenous steroids.

In an effort to evaluate the preceding observations a large group of patients with acute and chronic liver damage have received testosterone propionate and free testosterone and have been followed from the standpoint of 17-ketosteroid excretion prior to, during and following administration of testosterone. The results so obtained have been compared with similar studies in normal individuals.

In general it has been found that only those patients with considerable hepatic impairment show a significant abnormality in their ability to metabolize administered androgens to the physiologically less active compounds which are excreted as neutral 17-ketosteroids.

In a large group of patients with acute and chronic liver disease gynecomastia has been found to be a rare occurrence and to occur more commonly during convalescence than during the more severe phases of the disease. It is also the strong impression of the authors that in the rank and file of cirrhotic patients the loss of axillary and pubic hair and other endocrine abnormalities occur with only slightly greater frequency than is the case in a comparable group of patients who present an equal degree of debility from non-hepatic causes.

EFFECTS OF DESOXYCORTICOSTERONE IN RELATION TO ANTIDIURETIC FACTOR EXCRETION. *Julia Goodsell Skahen (by invitation) and D. M. Green, M.D., Seattle, Washington.* (From the University of Washington School of Medicine.)

Subcutaneous implantation of desoxycorticosterone in rats is followed by a prompt rise in fluid intake and subsequent elevation of blood pressure to hypertensive levels. Since upward disturbances in water balance presumably invoke responses by the posterior pituitary, studies were made of the effect of desoxycorticosterone on antidiuretic factor excretion and its relationship to changes in blood pressure.

Results indicated that the implantation of DCA pellets was followed both by hypertension and by increased antidiuretic factor excretion. However, the substitution of saline solution for drinking water in rats given no desoxycorticosterone also produced a rise in antidiuretic factor excretion but did not cause blood pressure elevation. In general, antidiuretic factor output appeared correlated with increased fluid intake,

regardless of the means used to stimulate a rise in voluntary fluid consumption.

The excretion of antidiuretic factor following desoxycorticosterone administration appeared to be a response to the drug-induced disturbance in fluid balance. No immediate relationship to the development of hypertension was demonstrated.

URINARY COPROPORPHYRIN EXCRETION IN PATIENTS WITH NEOPLASTIC DISEASES. *Howard R. Bierman, M.D., Louis A. Strait (by invitation) and M. Rhenoff (by invitation), San Francisco, California.* (From the Laboratory of Experimental Oncology, University of California Medical School.)

The twenty-four hour urinary coproporphyrin excretion has been studied in patients suffering from various neoplastic diseases. There appears to be a cyclic increase in excretion of coproporphyrin well beyond the present accepted limits of normal at regular periods in some patients who have been studied continuously for two to three months.

In eleven of sixteen instances administration of HN_2 in doses from 0.1 to 0.6 mg./Kg. body weight was followed by varying increases in coproporphyrin excretion over the pretreatment levels within twenty-four to ninety-six hours. There appears to be no relationship to the urinary volume.

Repeated daily doses of HN_2 in one patient exhausted the mechanism for increased coproporphyrin excretion after nine days.

Hematopoietic regeneration may be responsible for the coproporphyrinuria in some cases since there appears to be no correlation with hematopoietic or neoplastic tissue destruction. The possibility of an underlying neoplastic host mechanism may account for the periodic increase in coproporphyrin excretion unrelated to therapy.

LYMPHANGIOGRAPHY IN THE DIAGNOSIS OF CHYLANGIOMA AND LYMPHEDEMA. A PRELIMINARY REPORT. *Norman E. Freeman, M.D., San Francisco, California.*

Chylangioma and chylous fistula are rare conditions. Knapper in 1928 collected twelve cases from the literature and described one case of his own. In his patient the chylous fistula of the popliteal space was closed one year after resection of the pelvic lymphatics. Two cases of this condition have been encountered, one on the service of I. S. Ravdin at the University of

Pennsylvania Hospital and the second on the Children's Service at the University of California Hospital. In the former, studies were made on the fat content of the chyle obtained by puncture of a vesicle on the scrotum at intervals following ingestion of cream. In the latter the lymphatics of the pelvis, external genitalia and lower extremities were visualized by x-ray after injection of diodrast by direct puncture of a vesicle on the labia majora. It was shown that the valves of the lymphatics were deficient in this case. In both patients an attempt was made to resect the pelvic lymphatics. Although there was temporary improvement, in neither case was the condition completely relieved. The possibility of lymphangiography in the study of lymphedema is discussed.

ON THE CLINICAL USEFULNESS OF HYPOTONIC INTRAVENOUS SOLUTIONS. *F. R. Schemm, M.D., John A. Layne, M.D. and (by invitation) John S. Gilson, M.D., Great Falls, Montana.* (From the Department of Medicine, Great Falls Clinic.)

We have found hypotonic solutions given by vein effective in maintaining water balance when the administration of water *per se* was indicated and when the customary amounts of sodium chloride or dextrose found in isotonic solutions appeared undesirable. The hypotonic solutions, at first of two-thirds and later of one-half of isotonic strength, were particularly useful in postoperative or azotemic diabetic patients with cardiovascular-renal complications.

Hypotonic solutions have now been used in more than thirty-five instances, extending over periods of treatment from five to thirteen days. A total of from 1 to 4 L. were given daily, in volumes varying from 500 to 1,500 cc. at a time, with a rate of flow that ranged from 14 to 22 cc. per minute. One of the most useful solutions contained 2.25 Gm. of sodium chloride and 12.5 Gm. of dextrose in 1,000 cc. of water. With this latter solution, one can give, for example, with 4,000 cc. of water 50 Gm. of dextrose and 9 Gm. of sodium chloride in twenty-four hours. These amounts give a good base line for maintenance in, for example, postoperative diabetics with duodenal drainage, providing enough water and dextrose and not too much sodium. One-half isotonic strength saline or dextrose can be added or substituted for the combined solution when there appears to be need for more sodium or dextrose.

Studies of the blood immediately after administration of these hypotonic solutions or after several days' use of them showed no detectable dilution or disturbance of the electrolyte pattern of the blood, indicating how swiftly plain water is diffused throughout the 50 L. of total body water. In some instances these solutions were used in patients recovering from episodes of acute, profuse pulmonary edema.

MYOTONIA DUE TO COLD. A BENIGN SYNDROME OF MYOTONIC CONTRACTION AFTER EXPOSURE TO COLD MANIFESTING A CHARACTERISTIC HEREDITARY PATTERN. *Frank H. Tyler, M.D., Thomas A. Witten, M.D. and Fayette B. Stephens, Ph.D., (by invitation and introduced by Hans H. Hecht, M.D.), Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

The disease (paramyotonia congenita) described by Eulenberg in 1886 and by Rich in 1895 has not been clearly distinguished from other myotonias by most neurologists since that time. The opportunity to study a family with the disorder now presents itself. The syndrome consists of myotonic reaction occurring most frequently in facial, oculomotor and intrinsic hand muscles as the result of exposure to cold. Other factors are of little importance in the occurrence of the myotonia, but quick movement following rest or gross voluntary movement occasionally precipitate it in certain members of the family. The anomaly is present at birth and persists throughout life with a tendency to improvement not very marked and without the development of muscular atrophy and other degenerative changes.

A case of myotonic muscular contraction induced by exposure to cold or chilling is reported. A family history of sixty-two persons manifesting the disorder with a typical Mendelian dominant pattern of inheritance is presented. The myotonia responds to quinine in the same fashion as other myotonias.

CLINICAL AND LABORATORY RELIABILITY OF PROTEIN-BOUND BLOOD IODINE DETERMINATIONS. *Donald W. Petit, M.D. (by invitation), Paul Starr, M.D. and A. L. Chaney, Ph. D. (by invitation), Los Angeles, California.* (From the Department of Medicine, University of Southern California.)

Because of increasing acceptance of the usefulness of protein-bound blood iodine determina-

tions as an index of thyroid function, it was decided to subject the procedure used here to clinical test. A "blind" technic was used to find: (1) the reproducibility of results from identical specimens; (2) effect of an ordinary meal; (3) effect of mild exercise; (4) effect of ingestion of inorganic and organic iodine compounds; (5) the role of serum proteins in the final level of protein-bound blood iodine.

Ninety per cent of 112 specimens drawn from fifty-one subjects and tested in duplicate or triplicate agreed within 3 gamma per cent. Similar technics used for the testing of seventy-one specimens drawn from five normal males revealed no significant change in protein-bound blood iodine after meals or after mild exercise.

Serial determinations of protein-bound blood iodine in three patients receiving inorganic iodine solution revealed unreliable results during the ingestion of iodine and for forty-eight to seventy-two hours after its cessation. Isolated determinations on five patients after cholecystography revealed elevated protein-bound iodines for as long as three months after the drug had been administered. Similar tests on four patients who had had iodized oil introduced into the lung or subarachnoid space showed elevated levels of protein-bound iodine for periods in excess of one year. The finding of low protein-bound iodine levels in patients with low serum protein and apparently normal thyroid function deserves further study.

FACTORS INFLUENCING THE EFFECTIVENESS OF RADIOIODOTHERAPEUSIS. *Robert H. Williams, M.D., Seattle, Washington.* (From the Department of Medicine, University of Washington School of Medicine.)

The results of radioiodotherapeusis in 106 patients with thyrotoxicosis were found to compare favorably with the results of treatment by antithyroid drugs and subtotal thyroidectomy in 195 subjects and with the results of antithyroid drugs administered for prolonged intervals to 119 individuals.

The main problem in radioiodine therapy is in determining the optimum dosage. Although some indication of the quantity of isotope concentrated in the thyroid can be determined by estimating the rate of excretion of the radioiodine in the urine or by epithyroid counts, there are apparently many factors influencing the ultimate results of therapy, especially when I^{131} is used. Although the total amount of isotope localized in the thyroid is important, its

distribution in the acini is significant and factors influencing the turnover of iodine are also important.

Studies were made of the influence on iodine metabolism of adrenalin, trauma, bacterial toxins, halides, food, environmental factors, thiocyanate, propylthiouracil, adrenalectomy and thyroidectomy. The results of these studies and their possible influence upon radioiodotherapeusis are available for presentation.

THE HEART IN INFECTION. *Irving Fine, M.D. (by invitation), Henry Brainerd, M.D. and Maurice Sokolow, M.D., San Francisco, California.* (From the University of California Medical School.)

Eighty-four patients selected as being free of pre-existing heart disease, who were suffering from a variety of acute infectious diseases, were studied intensively to determine the nature and incidence of resulting abnormalities of the heart. The patients were subjected to serial clinical observations, determinations of venous pressure and circulation time and standard and unipolar electrocardiograms. An attempt was made to correlate clinical and electrocardiographic findings.

Thirty-three and three-tenths per cent of patients studied demonstrated definite abnormalities of the electrocardiogram at some time in the course of infection. These patients were suffering from typhoid, diphtheria, meningitis due to meningococci, pneumococci and *H. influenzae*, pneumococcal pneumonia, acute streptococcal infections and mumps. The commonest electrocardiographic abnormality was alteration of the T waves, followed by prolonged P-R interval, prolonged Q-T interval, arrhythmias, disturbed intraventricular conduction and S-T segment abnormalities in descending order of frequency. Eighteen patients subjected to artificial fever therapy did not exhibit similar changes.

Alterations of intensity or quality of the mitral first sound occurred in 46.4 per cent of patients with myocarditis as contrasted to 3.7 per cent of patients without myocarditis; this finding had the highest correlation of various clinical observations with electrocardiographic changes. Gallop rhythm was noted in 28.5 per cent of patients with myocarditis and occurred transiently in 7.2 per cent of patients without electrocardiographic abnormalities. Systolic murmurs occurred in 42.8 per cent of abnormal hearts but were heard in 25.9 per cent of individuals without demonstrable myocarditis.

The circulation time was markedly decreased by fever but was abnormal in only two patients with myocarditis. One patient with myocarditis exhibited elevation of the venous pressure.

EFFECTS OF THE ADMINISTRATION OF STREPTOMYCIN IN TREATMENT OF EXPERIMENTAL OBSTRUCTIVE APPENDICITIS. *H. A. Davis, M.D., J. K. Burns, M.D., (by invitation) J. D. Schuler, M.D. (by invitation), T. E. Wade, M.D. (by invitation) and A. B. Webber, M.D., Los Angeles, California.* (From the Hunterian Laboratory, the Department of Surgery and the Graduate School of Medicine, College of Medical Evangelists.)

In a study reported elsewhere it was demonstrated that a standard type of injury to the vermiform appendix of rabbits (devascularization with obstruction of 7 cm. from the tip) caused death in 80 per cent of untreated rabbits.

In order to study the effect of streptomycin upon the mortality rate five groups of rabbits were studied. The standard form of injury to the appendix was produced in all groups. Streptomycin in a dose of 50 mg. twice daily was injected subcutaneously for fourteen days. Streptomycin definitely lowered the immediate mortality rate from experimental obstructive appendicitis in rabbits, especially when administration was started within twenty-four hours after the lesion in the appendix was produced. The critical period during which a sharp rise in mortality occurs is delayed in streptomycin-treated rabbits and lies between twenty-four and forty-eight hours.

The rabbits were allowed to survive for a period of three months following discontinuance of streptomycin therapy. The incidence of residual abscess formation was high. The abscesses were usually small and apparently did not interfere with the health or nutrition of the animals. In a small number of animals the abscesses were very large.

STUDIES OF PLASMA QUINIDIN CONTENT IN RELATION TO SINGLE DOSE ADMINISTRATION, TOXIC MANIFESTATIONS AND THERAPEUTIC EFFECT. *Richard W. Kalmensohn (by invitation) and John J. Sampson, M.D., San Francisco, California.* (From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital.)

The purpose of this work is to present (1) the quinidin plasma levels after single doses of the drug given by the intramuscular route as compared to the oral and rectal routes, (2) the plasma quinidin content when toxic manifestations are exhibited by patients receiving the drug and (3) the levels at which conversion of auricular fibrillation to sinus rhythm occurs.

A new compound, quinidin lactate, was administered intramuscularly to six patients with normal hearts, two in single doses of 0.13 Gm. and four in doses of 0.6 Gm. In the latter dosage (0.6 Gm.) the curve of rise and fall of quinidin plasma levels reached a maximum content of 1.76 to 3.45 mg. per L. between one and two and two-third hours and fell to 25 to 50 per cent of the maximum in four hours and to 10 to 25 per cent in ten to twelve hours, with a small residual present in twenty-four hours. This compared with previous reports and our own observations in six patients using single oral doses of 0.6 Gm. quinidin sulfate, namely, 2.9 to 3.7 maximum content in one-half to four and one-half hours with an average of two and one-fourth hours and retention of about the same fall in plasma content at twelve and twenty-four hours. Rectal administration of 0.6 Gm. quinidin sulfate resulted in maximum levels of 0.51 to 1.19 mg. per L. with only a trace remaining in twelve hours.

Of the sixteen patients receiving test doses of quinidin by various routes two instances of hypotension were noted and these occurred only in the (four) patients given 0.6 Gm. quinidin lactate intramuscularly with maximum plasma content under 4.0 mg. per L. In the two instances in which hypotension developed during oral therapeutic use of quinidin sulfate the plasma contents were higher, namely, 6.9 and 8.1 mg. per L. This implies that administration of quinidin intramuscularly, as has been suspected from previous experience with its intravenous use, for reasons undetermined carries a greater risk than from oral or rectal use.

In six of fourteen instances of oral quinidin administered therapeutically the quinidin content of the plasma at which the various toxic manifestations first appeared varied from (1) 0.63 to 10.8 mg. per L. with nausea (five cases), diarrhea (three cases) and giddiness (three cases); (2) 4.86 and 12.68 with headache (two cases); (3) 8.1 and 14.5 with diplopia (two cases); (4) 3.65 and 8.1 with scotomas (two cases); (5) 14.5 with deafness (one case) and (6) 6.9 and 8.1 with hypotension (two cases).

Whereas gastrointestinal symptoms were the commonest initial evidence of toxicity, they accompanied tinnitus, deafness, scotomas and hypotension when the latter were present.

The quinidin content of the plasma of twelve patients at the time of conversion of auricular fibrillation to sinus rhythm varied from 7.48 to 23.7 mg. per L. in six instances of rheumatic heart disease (including three conversions of the same patient at 10.8, 11.7 and 14) and 3.30 to 5.67 in six patients with coronary arteriosclerosis with or without hypertension. Two patients had not converted at the time quinidin therapy was stopped because of significant hypotension.

QUANTITATIVE STUDY OF QUINIDINE THERAPY. *Maurice Sokolow, M.D. and (by invitation) Archie L. Edgar, M.D., San Francisco, California.* (From the University of California Medical School.)

The quantitative aspects of quinidine therapy were investigated by determining multiple blood and urine quinidine levels in forty-one patients on varying dose schedules. The photofluorimetric method of Brodie, as modified by Lilienthal, was used. Sinus rhythm was re-established in thirteen of fifteen cases of auricular fibrillation or flutter. The amount of quinidine required for conversion, using the two or four-hour schedule, varied from 1.2 Gm. in twenty hours to 9.3 Gm. in ninety-six hours, with maximum blood levels of 2.0 to 13.7 mg./L. and an average of 7.0 mg./L. In only two cases was the level required for conversion less than 4 mg./L. In one case converted with a level of 7 mg./L. relapse occurred on maintenance doses with a level of 3.8 mg./L.; reconversion resulted when a level of 5.5 mg./L. was obtained with higher doses. In the two failures levels of 10 and 11 mg./L. were attained. In one case of ventricular tachycardia approximately 4 mg./L. was found to be the critical blood level preventing recurrent attacks. Four relapses occurred when the level was 3.3, 3.5, 3.3 and 2.5 mg./L. Sinus rhythm was reestablished at levels of 4.1, 4.3, 5.6 and 4.6 mg./L.

The average net peak level (subtracting the morning residual level resulting from the previous day's therapy) obtained with 0.2 Gm. every two hours for five doses was 3.9 mg./L.; for 0.4 Gm. every two hours for five doses, 4.9 mg./L.; for 0.6 Gm. every two hours for five doses, 5.5 mg./L.

When fixed daily doses were given every

four or six hours, a plateau was reached within seventy-two hours; it lasted three to four days and was followed by a gradual decline. The increment in blood level from single added doses was found to be 0.8 mg./L. with 0.2 Gm.; 1.2 mg./L. with 0.4 Gm. and 1.9 mg./L. with 0.6 Gm. The increment progressively decreased after the first two or three doses when the same dose was given every two hours. Comparable blood levels were reached in six observations when oral and intramuscular quinidine were given to the same patient.

An average of 49 per cent of the last evening level was still present in the blood approximately twelve hours later. Urinary excretion accounted for only 10 to 20 per cent of the total daily dose. Measurable blood levels were found as long as seventy-two hours and urine levels as long as forty-eight hours after quinidine was discontinued.

TAP WATER SODIUM IN A LOW SALT DIET. *Seymour L. Cole, M.D. (by invitation and introduced by Edward Tyler, M.D.), Los Angeles, California.*

Drinking water has frequently been overlooked as a source of sodium large enough to be considered when restricting that element in the solid part of the diet to 0.5 to 1.0 Gm. day.

Analyses of the tap water of the Los Angeles County General Hospital show it to contain 25 to 30 mg. sodium per 100 cc. The factors responsible are the high salt content of the original source, the Colorado River, and addition of salt in the Metropolitan Water District and in the hospital itself for softening purposes.

Study of the low salt diets of Schemm, Schroeder and others reveals them to allow 1,000 to 2,500 cc. and more of drinking water per day. In addition there are 500 to 600 cc. of hidden water used in the cooking of rice and preparation of leafy vegetables. Thus, an intake of 3,000 cc. of drinking water containing 30 mg. of sodium per 100 cc. in itself would provide 900 mg. of the allowed 1,000 mg. of sodium.

Therefore, to attain a low salt diet distilled water or low sodium content water should be substituted for tap water of high sodium content in addition to other precautionary measures.

OBSERVATIONS CONCERNING THE RISE AND FALL OF FREE AND ESTERIFIED CHOLESTEROL IN RATS MADE HYPERCHOLESTEREMIC BY A NEW METHOD. *Meyer*

Friedman, M.D. and (by invitation) S. O. Byers, Ph.D., San Francisco, California. (From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital.)

It was found possible to increase immediately the total cholesterol content of the rat's plasma approximately 600 per cent above the normal level by the intravenous injection of a new preparation of free cholesterol.

Immediately following such injections into 122 rats (30 mg. of cholesterol per 100 Gm. of body weight), the plasma free cholesterol content rose from a preinjection level of 12 to 295 mg. per 100 cc. However, no immediate rise occurred in the plasma esterified cholesterol. Three hours after the injection the free cholesterol fell to a value of 122 mg. per 100 cc. where it remained for approximately twelve hours. At this same time, however, the esterified cholesterol content of the rat's plasma rose to a value approximately twice that of the pre-injection level and it remained at this increased concentration for over twenty-four hours. At the end of thirty-six hours both the free and esterified cholesterol content of the rat's plasma had returned to pre-injection levels.

By means of this new technic the rate of disappearance as well as the partial esterification of injected free cholesterol was studied in a quantitative fashion.

EFFECT OF ENVIRONMENTAL TEMPERATURE ON THE FEBRILE REACTION TO TYPHOID PARATYPHOID VACCINES AND OTHER PYROGENS. *R. Grant, Ph.D. (by invitation), Marilyn Robbins, A.B., (by invitation) and V. E. Hall, M.D., Palo Alto, California.*

The febrile response to intravenous injection of pyrogens in rabbits includes inhibition of the mechanisms for heat dissipation (polypnea and cutaneous vasodilatation) and moderate increase of heat production. Oxygen production is maximal about twenty minutes after injection, and the increase is about 15 per cent of the control value for the first hour. This metabolic response is uniform at environmental temperatures from 31°C. to -5°C. and in completely shorn animals at -5°C. although control levels of oxygen consumption are about 110 per cent higher than normal under the last conditions. During the second and subsequent hours of fever

at moderate and high environmental temperatures oxygen consumption usually remains slightly increased, but in animals exposed to severe cold oxygen usage shows sharp reduction below control values during the second hour associated with shivering. Recovery to normal or supranormal values follows during the third hour. In consequence of this inhibition of cold defense profound hypothermia develops following initial slight fever. At normal temperatures the second hour is marked by reduced inhibition of heat defense mechanisms or partial defervescence, and the third hour by renewed febrile genesis. Similar effects are obtained with an endogenous pyrogen ("Pyrexin").

ACUTE CORONARY ARTERY OCCLUSION ASSOCIATED WITH EARLY ELECTROCARDIOGRAPHIC FINDINGS SUGGESTIVE OF PREDOMINANTLY SUBENDOCARDIAL INJURY. A "NEW" PATTERN OF MYOCARDIAL INFARCTION. *Hans H. Hecht, M.D. and (by invitation) Leonard W. Ritzmann, M.D. Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

It is assumed that predominantly subepicardial lesions of the heart muscle are characterized by electrocardiograms which display inversion of T and elevation of the RT segment in leads dominated by the effects of epicardial regions. In these leads subendocardial injury is suggested by upright T waves and by depression of the RT segment. As the exploring electrode of a unipolar system is primarily influenced by the electrical changes of adjacent tissues and to a much lesser degree by alterations in the electrical state of remote regions, subendocardial lesions must be more extensive than subepicardial involvement if changes of equal magnitude are to be recorded by an epicardial electrode. This is demonstrated in human subjects when pressure injury by a venous catheter exerted over a region of a few mm. may cause a monophasic deformation of the endocardial electrocardiogram but which leaves a simultaneously recorded electrocardiogram of the subjacent epicardial surface unaltered.

These considerations are supported by observations on four patients, all with angina pectoris of many years' duration, who entered the hospital with the typical signs and symp-

toms of recent myocardial infarction. The electrocardiograms taken within a few hours of the onset of the attack revealed striking displacement of the ST segment downward and in the opposite direction from the usual pattern. The QRS complexes were increased in voltage and lacked the characteristic Q waves. In one patient the typical pattern of anterior myocardial infarction emerged after ten hours, in another deep inversion of the terminal portion of the T waves without ST segment changes replaced the original pattern.

All patients died and postmortem examinations were performed on three. The examinations revealed recent myocardial infarction of the anterior wall of the left ventricle caused by complete closure of the descending branch of the left coronary artery in each instance. Extensive narrowing of the remaining coronary arteries was present in all, with widespread diffuse and patchy fibrosis of the left ventricular musculature in addition to the recent infarction. Subendocardial necrosis was outstanding in all.

It is concluded that the electrocardiograms demonstrated extensive subendocardial injury of the anterior wall. The endocardial injury was excessive because extensive narrowing of the vascular bed prior to the final occlusion prevented adequate collateral circulation.

The peculiar electrocardiographic pattern is a poor prognostic sign when seen during an episode of acute myocardial infarction.

EXPERIMENTAL INTERAURICULAR SEPTAL DEFECTS. *Sanford E. Leeds, M.D., William Birsner, M.D. (by invitation) and Orrin Cook, M.D. (by invitation), San Francisco, California.* (From The Harold Brunn Institute, Mount Zion Hospital.)

The production of interauricular septal defects by surgical means may become important if it could be shown that patients with severe mitral stenosis would be benefited by such a procedure. Closure of large congenital auricular septal defects would be most advantageous if an entirely satisfactory technic could be devised. For these reasons an operation which could be done with low mortality and no loss of blood, was developed for production of interauricular septal defects in dogs. After producing the defects the animals were studied with the catheter technic.

MECHANISM AND EFFICACY OF DIBENAMINE PROTECTION AGAINST SPONTANEOUS CYCLOPROPANE ARRHYTHMIAS IN SURGICAL PATIENTS. *Mark Nickerson, Ph.D. (by invitation) Hugh O. Brown, M.D., and Scott M. Smith, M.D. (by invitation), Salt Lake City, Utah.* (From the Departments of Pharmacology and Anesthesiology, University of Utah College of Medicine.)

The subjects of this study were healthy young adults undergoing elective surgery. Premedication was given with barbiturate, morphine and scopolamine. Patients were uniformly carried through all planes of surgical anesthesia to respiratory arrest and back to plane I over a period of about thirty minutes with unsupplemented cyclopropane. In plane IV and stage IV adequate oxygenation was maintained by pressure on the rebreathing bag, except for short periods during which the effects of anoxia were observed. Continuous electrocardiographic tracings, usually lead II, were obtained.

Control patients developed arrhythmias in all planes of surgical anesthesia. These irregularities increased exponentially with the depth of anesthesia. Ventricular tachycardia regularly developed in plane IV or stage IV. The arrhythmias were found to be accentuated by anoxia.

Premedication (one-half to twelve hours prior to operation) with 5 mg./Kg. of dibenamine only slightly reduced the incidence and severity of arrhythmias, but 7.5 mg./Kg. almost completely eliminated them. Such irregularities as did occur tended to increase exponentially with the depth of anesthesia as in the control series. No serious untoward reactions were noted.

Dibenamine protection against cardiac arrhythmias does not appear to be merely secondary to the effects of the drug on the peripheral circulation. The mean blood pressure in the three groups during anesthesia was not significantly different and the dose of dibenamine required to prevent cardiac arrhythmias was definitely higher than the dose (5 mg./Kg.) required to reverse the blood pressure response to epinephrine or sympathetic nerve activity in humans.

HYPERSENSITIVITY TO PENICILLIN. *J. F. Waldo, M.D. and Jeanne T. Tyson, B.A. (by invitation and introduced by M. M. Winthrope) Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

In certain instances it has been possible to demonstrate by passive transfer, employing the Prausnitz-Küstner technic, a circulating antibody to penicillin. This passive transfer was possible only from those subjects with a severe reaction and then only during the most active phase of their reaction. The antigen employed for the passive transfer was crystalline penicillin dissolved in saline.

Experimental studies of penicillin sensitivity in animals are now in progress. By binding crystalline penicillin to pure human albumin we have been able to produce an antibody in rabbits which gives a fairly strong complement fixation reaction with the albumin-penicillin mixture after all reactivity to human albumin has been absorbed. Penicillin alone administered to the rabbit has failed to produce such an antibody. We also have some evidence that when penicillin is bound to human albumin the resulting antigenic product behaves in the manner of a mixed antigen while the human albumin used in the experiment behaves in the manner of a pure antigen. Quantitative studies of this antigen-antibody system are now in progress.

Inasmuch as it is known that penicillin does bind *in vivo* to albumin, it seems reasonable to suppose that when penicillin is administered to man the penicillin haptene coupled to albumin *in vivo* constitutes an antigen for the production of antibodies specific to this haptene group. This might well account for the penicillin sensitivity reactions that are observed in man.

EXCITATION OF HUMAN AURICULAR MUSCLE AND SIGNIFICANCE OF THE INTRINSICOID DEFLECTION OF THE AURICULAR ELECTROCARDIOGRAM. *Lowell A. Woodbury, Ph.D. (by invitation) and Hans H. Hecht, M.D., Salt Lake City, Utah.* (From the Departments of Physiology and Medicine, University of Utah College of Medicine.)

Electrocardiograms obtained by cardiac catheterization in man reveal a characteristic

form when the electrode is brought into contact with or closely adjacent to auricular muscle. The similarity of human records to those obtained from isolated muscle strips of lower animals is inescapable. It stimulated the re-examination of the "dipole" concept of the membrane theory of cardiac excitation and recovery.

Theoretical considerations support this concept. The wave of excitation may be viewed as a band in which the membrane is partially depolarized. The band is not sharply demarcated but shades from complete polarization on the leading edge to complete depolarization on the following edge. This is equivalent to two line charges of opposite sign the effective width of the band apart and submerged in a volume conductor. If a model is constructed or if the circles of equipotentials that arise from the two line charges are plotted and if a point representing the electrode is placed so that the moving line charges pass under or very close to the point, a diphasic curve may be constructed geometrically and expressed mathematically. The theoretical curve very closely resembles the recorded action potentials from human auricular muscle *in situ*.

Practical considerations deal with the definition and clinical application of the intrinsic deflection of Lewis which defines the moment that the band begins to pass under the electrode and the semidirect or intrinsicoid deflection of Wilson that defines a similar event for semi-direct leads. It is demonstrated that with the exception of certain esophageal positions no true intrinsicoid deflection and no truly semi-direct leads exist for auricular muscle in man. The impact of these considerations for the diagnosis of auricular enlargement and for the so-called pattern of mitral and pulmonic P waves will be discussed on the basis of observations obtained from detailed analysis of simultaneously recorded esophageal and precordial auricular leads.

Case Report

Chiari's Syndrome—Obliterative Endophlebitis of the Hepatic Veins*

HILARY H. HOLMES, M.D. and GEORGE MELCHER, M.D.

New York, New York

THE term Chiari's syndrome has been loosely applied in the past twenty years to many diseases in which there is obstruction or thrombosis of the hepatic veins, regardless of the underlying etiology. Chiari,¹ in 1899, described three cases which he believed fell into a separate pathologic entity, i.e., primary obliterative endophlebitis of the hepatic veins. He also included in his paper seven other cases in which the cause of death was an obliterative thrombosis of the hepatic veins but in which the thrombosis was thought to be secondary to another etiologic basis, e.g., peritonitis, congenital malformation of the hepatic veins, cirrhosis, etc.

Although Budd² first reported a case of hepatic vein occlusion, he recorded very few clinical details of the patient's course. The autopsy findings of peritoneal, pleural and pericardial adhesions which he described are compatible with the findings in polyserositis as the underlying cause of the occlusion.

Thirteen cases of hepatic vein thrombosis have been found in 15,300 consecutive autopsies performed by the Department of Pathology of Columbia University, but the one reported herein is the only one which falls under the heading of Chiari's syndrome as he described it. The lesions associated with hepatic vein obstruction in the other patients were carcinoma in four, sarcoma in two, liver abscesses in three, operative procedure in one (porta-caval shunt), cavernomatous transformation of

the portal vein in one and polycythemia vera in one. Any lesion which may involve the hepatic veins due to proximity or which causes generalized thrombosis, such as neoplasms, scars, inferior vena caval thrombosis, abscesses, gummas, enlarged lymph nodes, polycythemia vera and many others, may produce occlusion of the hepatic veins. Recently all of these diseases have been lumped together under the term Chiari's syndrome (Budd's syndrome might be more appropriate as Chiari distinguished between this secondary type of obstruction and that due to primary thrombosis).

The basis for primary obliteration of the hepatic veins has not been adequately explained. Chiari believed that the underlying process was an inflammation of the vein wall whereas Thompson and Turnbull³ suggested thrombophlebitis as its cause, the changes in the vein walls being secondary to the thrombi. Satke⁴ reported four cases of obliterative endophlebitis of the hepatic veins, and he presented histologic evidence for Chiari's contention that the primary change is thickening of the endothelium of the vein wall and that thromboses are secondary. Kelsey and Comfort⁵ summarized the theories for the predilection for the hepatic veins as a site for thrombosis. They pointed out that retardation of flow at the diaphragmatic level by pressure changes in the thorax along with mechanical factors at the ostia of the veins which suspend the liver from the vena cava might be factors in the pathogenesis of thrombosis. Other hypotheses include Rosenblatt's⁶ idea of

* From the Departments of Medicine and Pathology, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York, N. Y.

congenital occlusion of the hepatic veins, and Moore's⁷ theory of reactivation of the tendency to obliteration such as occurs in fetal ductus venosus. Hutchinson and Simpson⁸ suggested that the intra-uterine obliteration of the venae revehentes might continue too far. Whatever the pathogenesis, hepatic vein occlusion is extremely rare and invariably fatal.

Hirsh and Manchester⁹ summarized 'the seventy cases reported up to 1946 and discussed the various causes of obstruction of the hepatic veins. They pointed out that there is an acute and a chronic form of the disease, depending upon whether the occlusion is partial or complete and whether recanalization occurs. Although the disease may occur at any age, over 50 per cent of the reported cases occurred between the ages of twenty and forty. Both sexes are equally affected.

The clinical symptoms reflect the rapidity of the process of occlusion. Invariably the first symptom is abdominal pain or discomfort, most marked in the upper abdomen. This may continue for months before the patient seeks medical assistance, or it may be sudden and severe. Abdominal enlargement is usually noted by the patient or his friends. A history of icterus is unusual. In cases of several months' duration peripheral edema is usually present.

The acute form and the terminal episode in the chronic form of the disease is that of severe upper abdominal pain resembling an abdominal catastrophe, vomiting and rapid enlargement of the abdomen. Upon examination the patient is usually in shock. There is splinting of the abdomen, marked enlargement and tenderness of the liver, ascites and splenomegaly, again depending upon the rapidity of occlusion. Mild icterus and acidosis may now be present. Coma rapidly ensues and death due to hepatic insufficiency occurs within a few hours to a few days.

Experimentally, the syndrome has been reproduced in animals. Simonds and Callaway¹⁰ produced sudden complete obstruction of the hepatic veins in dogs, causing

marked enlargement of the liver, shock and rapid death similar to the pattern in Chiari's syndrome.

The case to be described very closely resembles the first of the three cases which Chiari described, and the autopsy findings are typical of the other cases reported in the literature.

CASE REPORT

A. F., a twenty-three year old white female proof-reader, was transferred in coma to the Presbyterian Hospital from the Muhlenberg Hospital in Plainfield, N. J., on April 22, 1947.

Her past history, taken from the patient at that hospital, revealed vague abdominal pain, gradual enlargement of her abdomen and a weight gain of 23 pounds over the past year. Her diet had been deficient in protein and her alcoholic intake had been excessive for more than two years. Six months before admission she had fallen from a horse and sustained a head injury with a large facial hematoma but had not lost consciousness or had any other signs of central nervous involvement. In 1942 she had an attack of primary atypical pneumonia from which she recovered completely. During the past few months she had had several attacks of upper abdominal distress, the last episode being one month before when she had experienced rather severe epigastric pain, anorexia, nausea and vomiting. This attack lasted only twenty-four hours. At no time had she been noted to have any signs, symptoms or hematologic findings of polycythemia vera. She had not been exposed to hepatotoxins or jaundiced persons. Six days before admission she had been vaccinated with smallpox vaccine.

The onset of her present illness was forty-eight hours before admission to the Muhlenberg Hospital when during the morning she began to have intermittent upper abdominal "gas" pains. Shortly after the onset the pains became generalized throughout her abdomen and were moderately acute. The following day she experienced some nausea and vomiting and took several enemas, productive of brown stools, with temporary relief. About one hour after her evening meal on the second day of her illness the pains and vomiting recurred with increased severity.

A physician was called at that time and he noted that her liver was enlarged. He administered a sedative and advised hospitalization.

However, she remained at home and was seen again the following morning. At this time she was in profound shock and was immediately hospitalized.

Upon admission to the Muhlenberg Hospital her temperature was 94.4°F., apical pulse 88, respirations 32 (regular). The blood pressure was unobtainable. She was somnolent and slightly cyanotic although she was sufficiently alert to give a satisfactory history. She complained of drowsiness, shortness of breath and pain in her right shoulder since early morning. Her pupils were constricted and reacted sluggishly to light. The fundi showed engorged veins. The only other positive physical findings were a distended abdomen containing a fluid wave, liver enlarged to 8 cm. below the costal border and spleen enlarged to 5 cm. below the costal border. No peripheral pulses were palpable.

Admission studies revealed the following: hemoglobin 21 Gm. (145 per cent); red blood cells 11,680,000; white blood cells 44,900 (neutrophils 89, lymphocytes 11, eosinophiles 1); hematocrit 85 per cent (checked on two specimens of blood); non-protein nitrogen 67 mg. per cent; serum uric acid 5 mg. per cent; cholesterol 210 mg. per cent; icterus index 8; serum chlorides 400 mg. per cent; CO₂ 28 volumes per cent; serum proteins 11.4 Gm. per cent (by the copper sulfate method and checked by the Kjeldahl method); urine albumin 4 plus, with occasional red blood cell and white blood cells in the microscopic examination.

A 500 cc. phlebotomy was performed and 1,500 cc. of saline administered. Shortly after the phlebotomy and the infusion of saline a repeat count showed that the red blood cells had fallen to 8,320,000, hemoglobin to 20.7 Gm. and hematocrit to 77 per cent. Leukocytosis increased to 62,400 with 89 per cent neutrophils. The blood smear was reported to show 2 per cent myelocytes, many large platelets but no myeloblasts.

During the day her blood pressure ranged from 80/60 to 118/80. Her temperature rose to 100.2°F. during the evening of the first day in that hospital. She was very restless all day but no sedatives were administered. Heparin, 10 mg., was given intravenously soon after admission, and another 15 mg. within three hours, but no venous clotting times were recorded.

Twelve hours after admission, following intravenous administration of 3,000 cc. of 5 per cent glucose in water, the total protein had

fallen to 5.75 Gm. A blood count then showed further reduction of red blood cells to 7,800,000 and a hemoglobin of 17.5 Gm. (120 per cent). At that time she was rational, with less discomfort and was sitting up talking to her family. Later that evening she lapsed into a coma and on the following morning, April 22, 1947, she was transferred to the Presbyterian Hospital. Immediately prior to transfer the red count was 6,350,000, white blood cells 28,600 (89 per cent neutrophils) and hematocrit 55 per cent. Other laboratory reports from that hospital showed a slightly positive reaction for blood in her feces and vomitus.

Physical examination upon admission to Presbyterian Hospital revealed a dark-complexioned, young adult female in a deep coma. Her temperature was 98.2°F., pulse 100, respirations 28, and blood pressure in the left arm 112/80. She responded only to painful stimuli. Her skin was cool and moist, with no eruption, petechiae, cyanosis or jaundice but had a peculiar alabaster hue. Her entire body seemed edematous but no pitting could be made out. She was breathing deeply, and an "amine odor" was noted on her breath. The pupils were widely dilated, equal and reacted sluggishly to light. Her conjunctivae were injected and the right cornea had a small abrasion over its surface. Her sclerae were not icteric and the fundi were normal. The jaw was held rigidly in trismus; her tongue was abraded from bites and she was intermittently grinding her teeth together. Ear, nose and throat examination was otherwise normal. The neck was supple and glandular adenopathy was not present. The lungs were clear. The heart was not enlarged; there was regular sinus rhythm; sounds were of good quality. No murmurs were heard and A₂ equalled P₂. The abdomen was distended and a fluid wave was present. The liver was enlarged to 5 finger-breadths below the costal margin, was firm, not nodular and pressure over it caused groans from the patient. The spleen could not be palpated and no other masses or organs were noted. Rectal examination was negative and the stool specimen obtained was brown and guaiac negative. The extremities exhibited intermittent episodes of spasm or tonic contractions. Reflexes were equal and active throughout and inconstant Babinski signs were present. The abdominals and ankle jerks were absent. The Chvostek sign was positive but the Trousseau was negative.

Laboratory findings on admission were: hemoglobin 17.5 Gm.; red blood cells 5,500,000; white blood cells 43,500 with 92 per cent neutrophils; platelets 668,000; erythrocyte sedimentation rate 0; hematocrit 60.9 per cent; urine specific gravity 1.008, acid reaction, albumin 3 plus, glucose negative, bile negative and upon microscopic examination 10 to 12 red blood cells per high power field as well as 40 to 50 white blood cells per high power field were seen. Serum urea nitrogen 36 mg. per cent; serum sugar (with 5 per cent dextrose infusion running into the opposite arm) 133 mg. per cent; alkaline phosphatase 9.5 Bodansky units; serum bilirubin 2.3 mg. per cent; cholesterol 61 mg. per cent; cephalin flocculation 4 plus; serum protein 4.6 Gm. per cent (albumin 4.0 and globulin 0.6); Kline test negative; serum amylase 44 Myers and Killian units; prothrombin time 35 seconds (normal 14 ± 1 seconds); CO_2 41.5 volumes per cent; serum chlorides 86.7 mEq./L.; serum calcium 8.3 mg. per cent; venous clotting time three minutes and forty-five seconds; blood culture showed no growth; x-ray of the chest revealed no evidence of pulmonary disease; x-ray of the abdomen showed ascites, with a single gas-filled loop of small intestine on the right side. The patient was seen by a surgical consultant who thought that there were no indications for abdominal exploration. A neurologic consultant agreed that her central nervous system symptoms were undoubtedly due to hepatic insufficiency but added that postvaccinal encephalitis might also be complicating the picture. A lumbar puncture was done, with normal pressure findings and no cells were found in the spinal fluid.

She remained in a deep coma and was treated with 600 cc. of plasma and almost continuous intravenous glucose which was administered slowly. Eight hours after admission the hematocrit had fallen to 54 per cent. She was also given penicillin in a dosage schedule of 100,000 units every three hours. She was catheterized every six hours, but only 110 cc. of urine were obtained over the twenty-three hour period. Twenty hours after admission it was noted that she was definitely icteric, that the liver was larger by 2 finger-breadths, the spleen was palpable and more ascites had accumulated. Her urine showed 1 plus bile. Blood studies then showed a hematocrit of 49 per cent; alkaline phosphatase of 10.2 Bodansky units; bilirubin 3.4 mg. per cent; serum urea nitrogen

53 mg. per cent and serum amino acid nitrogen of 5.5 mg. per cent.

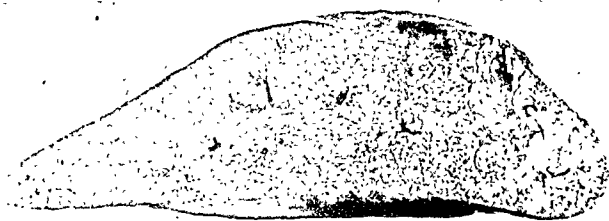
Her course was progressively downhill and her temperature rose to 102.8°F . Twenty-three hours after admission she suddenly became cyanotic and ceased breathing.

The significant findings at autopsy were the following: Grossly, the abdomen was moderately distended. When the incisions were made, the subcutaneous tissues of the trunk and body musculature appeared to be water-logged. Two hundred cc. of clear yellow fluid were found in each thoracic cavity, 2 liters of fluid of a similar nature were present in the peritoneal cavity. Large masses of coagulated protein material were pulled away from the retroperitoneal spaces. The heart weighed 260 Gm. and was not remarkable, except for three small, stringy clots in the right auricle and ventricle.

The lung surfaces were wet and mottled, purple-red and yellow. There was moderate congestion and edema on section, and the base of the right lower lobe was atelectatic.

The spleen was markedly enlarged, weighed 620 Gm. and was more firm than usual. Throughout its substance could be seen a few whitish nodules averaging 2 mm. across. One larger nodule raised the capsule slightly. All appeared spherical on section.

The liver was markedly enlarged and weighed 2,500 Gm. The whole organ had the usual consistency. Its color was derived from two elements: confluent, irregularly rounded, yellow spots averaging 2 mm. across and standing out against the dark purple background. Upon section the details were clearer, with yellow portions projecting above the dark, bloody background, suggesting swollen lobules surrounded by hemorrhagic and necrotic stroma. Throughout the parenchyma, white, firm, fibrous, cord-like structures were encountered on multiple section, the manner of their branching suggesting blood vessels. Occasionally the structure of a vein could be discerned, occluded with connective tissue and sometimes partially canalized. Another lesion seen on multiple section was an irregular, opaque, soft mass of tissue of a paler yellow, through the center of which there was a vein occluded by a thrombus. A similar soft thrombus was found adherent to the wall of one of the main intrahepatic branches of the portal vein, with other thrombi found in the lumen of the portal vein as it was followed into the mesentery. (Figs. 1 and 2.)



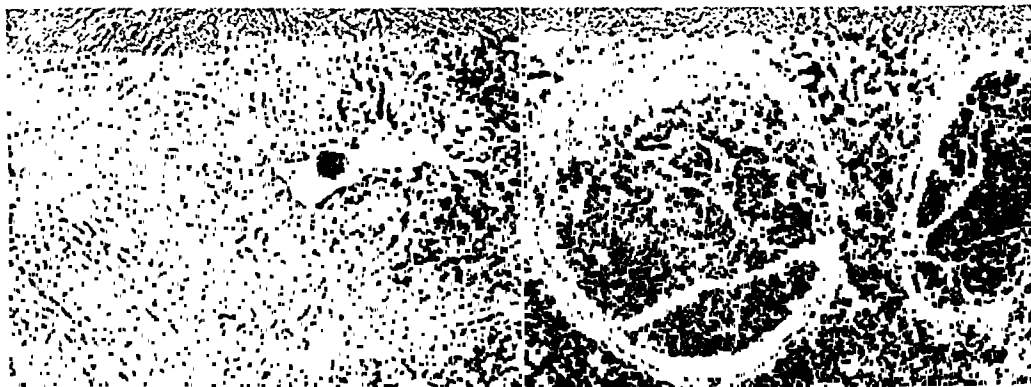
1



2

FIG. 1. Gross appearance of liver. Thrombi are present in nearly all of the larger hepatic vein radicles. In the center of the infarct on the right is a vein occluded by a thrombus.

FIG. 2. Another section of liver showing extreme congestion, patchy infarction and thrombosis.



3

4

FIG. 3. Low power microscopic section of the liver. The sparing of the periportal areas by the hemorrhagic coagulative necrosis is well illustrated.

FIG. 4. This low power section shows two hepatic vein radicles partially occluded by recent thrombi, some inflammatory reaction within the vein walls and necrotic liver parenchyma adjacent to the veins.

The kidney cortices were unusually homogeneous, smooth, red-brown in color and without distinguishing landmarks. The capsules stripped easily, and the pelves and calyces were not remarkable. The right ovary contained a 2 cm. cyst. The intestinal wall was thickened with edema and its mucosa was congested.

The thyroid and the bone marrow were not unusual, except that they were redder than is ordinarily found.

The gyri of the cerebrum were slightly flattened and the sulci correspondingly narrowed throughout. Otherwise, there were no remarkable gross findings.

The significant microscopic findings were the following: The heart showed an area of diffuse hemorrhage in the myocardium close to the epicardium of the left ventricle. A small, free thrombus was noted adjacent to the endocardial surface of the right ventricle and its sectional outline was rounded, suggesting an origin within a small vessel.

In the lungs there was a slight amount of coagulated protein material in certain alveoli.

Many alveoli were filled with red blood cells. Small thrombi were found in many of the smaller pulmonary artery radicles, one showing almost complete organization.

The spleen showed chronic congestion, and section through the largest aspect of the subcapsular whitish nodule showed it to be circumscribed. It compressed the adjacent parenchyma, indicating expansile growth. The small tumor was composed of tissue resembling red pulp, with exaggerated sinusoidal walls, containing no Malpighian corpuscles. It was considered to be a benign hamartoma.

In the liver there was widespread congestion and hemorrhagic coagulative necrosis which, as a rule, spared the periportal areas. Thrombi were found in the hepatic veins, frequently attached to their walls. (Figs. 3 and 4.) There was marked inflammatory reaction in the walls of some small veins. A large vein, half-occluded, showed strands of pink-staining fibrin-like material in its wall. The wall was thin at several points and at one point was broken and a patch of new fibrous tissue was present. Outside some

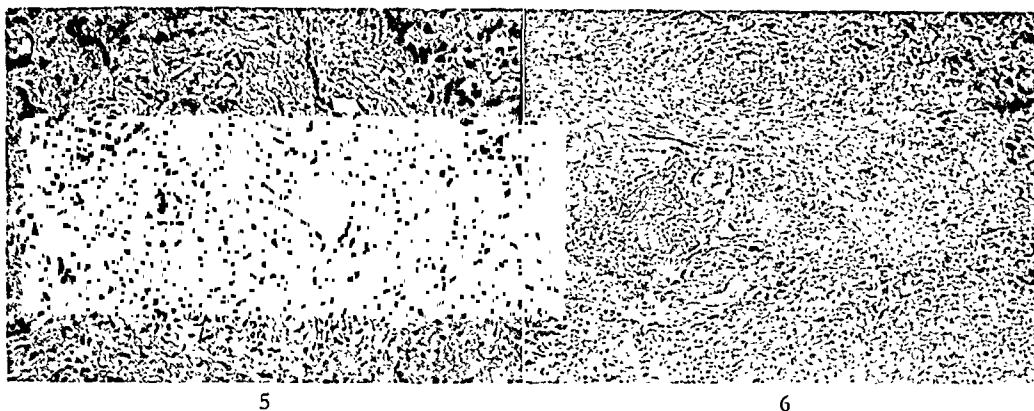


FIG. 5. A high power view of a thrombosed vein in which complete organization and recanalization have occurred.

FIG. 6. In this section there is a vein partially occluded by an old, organized thrombus with superimposed fresh thrombosis.

of the veins the connective tissue was quite edematous. Some veins were completely organized and showed varying degrees of canalization. (Figs. 5 and 6.)

The kidneys had congested glomeruli. The convoluted tubules contained a granular precipitate and appeared slightly distended. The proximal convoluted tubular cells projected into the lumina. The cytoplasm of all the cells was homogeneous and granular. In the collecting tubules masses of granular, red-staining material were seen. One of the pelvic veins showed an edematous wall and contained several rounded pieces of thrombus.

The bladder was not remarkable except for occlusion of a small artery by fibrous tissue. A vein in one of the Fallopian tubes was blocked and distended by a thrombus as were one artery and several veins in the ovaries and mesovarium. There were veins in the mesentery containing thrombi either completely or partially occluding them.

The stomach, small intestine and colon showed edema of the muscular layers and occasional veins containing fragments of thrombi.

The bone marrow showed an increase in the megakaryocytes in all fields.

The only lesion of note in the brain and spinal cord, other than a congenital extradural cyst with herniation of the arachnoid membrane at the eighth thoracic vertebral level, was congestion and edema of the brain.

Anatomic diagnoses were as follows: thrombi in the hepatic veins; thrombi in many small veins, generalized; necrosis of the liver; ascites and hydrothorax, bilateral; edema of the brain; emboli in the smaller pulmonary arteries;

increase in the bone marrow megakaryocytes; benign hamartomas of the spleen.

COMMENTS

The case herein reported, of obscure etiology, is believed to be fairly typical of the independent obliterative endophlebitis of the hepatic veins seen in the three cases described by Chiari,¹ and in several of the cases reported by Hess¹¹ and Satke.⁴

The sudden terminal episode of severe abdominal pain, shock of an extreme nature, and coma and death due to hepatic insufficiency was due undoubtedly to the final, almost complete occlusion of the hepatic veins resulting in massive congestion and necrosis of the liver parenchyma.

The intermittent bouts of upper abdominal pain and abdominal swelling in the months prior to the final episode were probably associated with the inflammatory process in the hepatic veins and occlusion of smaller radicals. The history of trauma six months before death must be considered to have a possible rôle in the etiology, but there were no immediate abdominal symptoms nor were there any in the two months following her accident. Thrombosis of the hepatic veins is one of the most serious complications of polycythemia vera,¹² and in this case that diagnosis was suggested in the beginning because of the extreme hemoconcentration. It was believed that this dyscrasia was ruled out by the fact that

she had never had any suspicion of polycythemia previously, that her plasma proteins were 11.4 Gm. per cent when she was polycythemic and on subsequent hydration fell even to below normal limits, that she was in profound shock at the time her high red count and hematocrit were taken and that her bone marrow was not hyperplastic on microscopic examination.

Thromboses occurred in many other vessels throughout the body in addition to those in the hepatic veins, and somewhat similar findings have been seen in the syndrome of acute febrile anemia and thrombocytopenic purpura with capillary platelet thromboses described by Moschkowitz¹³ and Baehr.¹⁴ However, the elevated platelet count in this case and the absence of purpura, anemia and generalized capillary and precapillary hyaline thrombi differentiates this case from those. The complete intrahepatic thromboses and massive necrosis of the liver make the thromboses elsewhere in the body assume only secondary importance although they are undoubtedly based upon the same etiology whatever that may be.

Sproul¹⁵ reviewed the occurrences of multiple venous thromboses in carcinoma of various sites, especially in the body and tail of the pancreas, but in the absence of carcinoma this warrants only passing consideration in the differential diagnosis of this unusual lesion.

SUMMARY

A case of Chiari's syndrome, idiopathic obliterative endophlebitis of the hepatic veins, is presented with the clinical and pathologic findings.

A distinction is made between obliterative endophlebitis of the hepatic veins as seen in this syndrome and occlusion due to other

intrahepatic or extrahepatic diseases in which the hepatic veins are secondarily involved.

REFERENCES

1. CHIARI, H. Über die selbständige Phlebitis obliterans der Hauptstämme der Venae hepaticae als Todesursache. *Beitr. z. path. Anat. u. z. allg. Path.*, 26: 1-18, 1899.
2. BUDD, G. On Diseases of the Liver. 1st ed., p. 152. Philadelphia, 1846. Lea and Blanchard.
3. THOMPSON, T. and TURNBULL, H. M. Primary occlusion of ostia of hepatic veins. *Quart. J. Med.*, 5: 277-296, 1912.
4. SATKE, O. Endophlebitis obliterans hepatica. *Deutsches Arch. f. klin. Med.*, 165: 330-353, 1929.
5. KELSEY, M. P. and COMFORT, M. W. Occlusion of hepatic veins: review of twenty cases. *Arch. Int. Med.*, 75: 175-183, 1945.
6. ROSENBLATT, O. G. Über einen Fall von abnormen Verlauf der Lebervenen in Verbindung mit Cirrhose und Carcinom der Leber und consecutiver carcinomatöser Infiltration des Peritoncums. *Jahresb. u. d. Leistung. d. ges. Med.*, 1: 226, 1867.
7. MOORE, F. C. Primary obliterative inflammation of main trunks of hepatic veins. *M. Chron.*, 3: 240-251, 1902.
8. HUTCHINSON, R. and SIMPSON, S. L. Occlusion of hepatic veins with cirrhosis of liver. *Arch. Dis. Childhood*, 5: 167-186, 1930.
9. HIRSH, H. L. and MANCHESTER, B. Chiari's syndrome: report of a case. *New England J. Med.*, 235: 507-511, 1946.
10. SIMONDS, J. P. and CALLOWAY, J. W. Anatomical changes in livers of dogs following mechanical constriction of hepatic veins. *Am. J. Path.*, 8: 159-166, 1932.
11. HESS, A. F. Fatal obliterating endo-phlebitis of hepatic veins. *Am. J. M. Sc.*, 130: 986-1001, 1905.
12. SOHVAL, A. R. Hepatic complications in polycythemia vera, with particular reference to thrombosis of hepatic and portal veins and hepatic cirrhosis. *Arch. Int. Med.*, 62: 925-945, 1938.
13. MOSCHCOWITZ, E. An acute febrile pleiochromic anemia with hyaline thromboses of the terminal arterioles and capillaries. *Arch. Int. Med.*, 36: 89, 1925.
14. BAEHR, G., KLEMPERER, P. and SCHIFRIN, A. Acute febrile anemia and thrombocytopenic purpura with platelet thromboses in capillaries and arterioles. *Tr. A. Am. Physicians*, 51: 43, 1936.
15. SPROUL, E. E. Carcinoma and venous thrombosis: the frequency of association of carcinoma in the body or tail of the pancreas with multiple venous thromboses. *Am. J. Cancer*, 34: 566-585, 1938.

Editorial

New Antibiotics

WITHIN the past year three new antibiotics have been announced for the treatment of certain infections that have failed to respond to penicillin or streptomycin. They are chloromycetin, aureomycin (Duomycin) and bacitracin.

Great interest has been focused on chloromycetin,¹ especially in the treatment of rickettsial diseases (epidemic typhus, scrub typhus, Rocky Mountain spotted fever and Q fever) and typhoid fever. There seems to be little doubt that this new antibiotic is highly effective in all of the human rickettsial diseases that have been studied. The duration of the disease is definitely shortened following its use and the clinical course is changed in a striking manner within twenty-four to seventy-two hours after chloromycetin is started. Chloromycetin is effective when given by mouth and the side effects are minimal.

In typhoid fever the results of treatment with chloromycetin have been extremely impressive. When treatment was started in the first two weeks of the disease, the average duration of fever was only 3.5 days after treatment was started. The average duration of the febrile course of the disease in the treated cases was approximately 12.5 days, whereas in a control group of patients who received no chloromycetin the average duration of the disease was thirty-five days. The difference in the

duration of the disease in these two groups therefore was very significant.

In addition to the rapid decrease in the fever there was evidence of improvement in the general condition of the patient and a decrease in the signs of intoxication within twenty-four hours. The bacteremia was cleared permanently in eight of ten cases. Chloromycetin in the doses that were used did not prevent relapses nor complications such as perforation and hemorrhage, even in the afebrile period of the disease. Relapses responded to further chloromycetin therapy.

It is plain, then, that chloromycetin alters the clinical course of typhoid fever but with the dosage schedules that have been used so far relapses and complications even during the afebrile stage of the disease following treatment have not been prevented. Optimal dosage schedules should be explored further.

The *in vitro* bacterial spectrum shows that chloromycetin is effective in small concentrations against many gram-positive and gram-negative organisms. Moderately high concentrations are required for certain gram-negative bacilli and mycobacteria. It is ineffective against rabbit syphilis, protozoa and various fungi. It has been effective against the growth of some strains of psittacosis in eggs and mice. It does not have any effect against pneumococcal infections nor against various experimental virus infections in mice. It is quantitatively inferior to streptomycin against many bacterial infections in mice.

So far as the information goes at present

¹ WOODWARD, T. E., SMADEL, J. E., LEY, H., JR., GREEN, R. and MANKIKAR, D. S. Preliminary report on the beneficial effect of chloromycetin in the treatment of typhoid fever. *Ann. Int. Med.*, 29: 131, 1948.

the greatest field of usefulness for chloromycetin would appear to be in the treatment of rickettsial infections and in typhoid fever. Further clinical studies are needed to define its place in the treatment of other bacterial infections and in virus infections.

Aureomycin² has been used with great success in the treatment of human cases of acute brucellosis, lymphogranuloma venereum, Rocky Mountain spotted fever, Q fever and in typhus fever. Some patients with urinary tract infections that were resistant to penicillin and streptomycin have responded favorably to aureomycin (*Bacillus coli*, *aerogenes*, *Bacillus paracolon*, *Streptococcus faecalis*). There is evidence from the study of experimental infections in animals that rickettsial infections and the psittacosis viruses respond favorably to its action. Bacterial infections of the conjunctivae caused by staphylococci, pneumococci and *Hemophilus influenzae*, *diplobacillus* of Morax-Axenfeld and Friedländer's bacillus have been reported to respond favorably following the local use of aureomycin (aureomycin borate, 0.5 per cent concentration). Inclusion conjunctivitis, follicular conjunctivitis and herpes simplex of the cornea also have cleared under treatment.

The favorable response of some patients with primary atypical pneumonia following aureomycin has been very striking. The temperature declines and the signs of intoxication regress in a period of thirty-six to seventy-two hours after the drug has been given. This is of great interest since

up to the present time aureomycin has not been found to be effective in any proved virus infection. It is also ineffective in *Proteus vulgaris* and *Pseudomonas aeruginosa* infections but its effect in *Salmonella* and typhoid infections is questionable.

In brief, then, both aureomycin and chloromycetin have proved to be highly effective in rickettsial infections. In addition chloromycetin has a striking effect in typhoid fever whereas the effect of aureomycin in this disease is questionable. Aureomycin influences lymphogranuloma venereum, acute brucellosis and some cases of primary atypical pneumonia and urinary tract infections in a favorable sense and it has been used in penicillin- and streptomycin-resistant bacterial infections that are sensitive to aureomycin.

Bacitracin³ has been useful in the treatment of wound and ocular infections that are resistant to penicillin. Due to the fact that it has been difficult to prepare bacitracin that is free of renal toxic factor, its use at present is limited to the treatment of local infections with solutions or ointments.

It can be said that great advances are being made every year in the war against infections. One infection after another can now be treated with anti-infective agents that were non-existent ten years ago. It is not too much to expect that the search for new agents now in progress will yield additional remedies that will aid in the treatment of infections that cannot be controlled at the present time.

CHESTER S. KEEFER, M.D.

² Aureomycin—A New Antibiotic. (A series of sixteen articles by forty-three authors.) *Ann. New York Acad. Sc.*, 51: 175-342, 1948.

³ MELENEY, F. L., ALTEMEIER, W., LONGACRE, A. B., PULASKI, E. J. and ZINTEL, H. A. The results of the systemic administration of the antibiotic, bacitracin, in surgical infections. A preliminary report. *Ann. Surg.*, 128: 714-731, 1948.

Aureomycin in Typhus and Brucellosis*

VERNON KNIGHT, M.D.,† FRANCISCO RUIZ-SANCHEZ, M.D., AMADO RUIZ-SANCHEZ, M.D.
and WALSH McDERMOTT, M.D.

New York, New York

IN the summer of 1948 in the course of an investigation of the antimicrobial therapy of typhoid fever with various drugs, eleven patients with typhus† and five with brucellosis were treated with aureomycin. The studies were conducted in Mexico by a group of investigators from the University of Guadalajara and the New York Hospital-Cornell University Medical College. As a striking improvement occurred uniformly in the typhus and brucella infections immediately after the start of therapy, observations on these cases are reported at this time. The results of the typhoid study will be presented in a subsequent report.¹

TYPHUS FEVER

Clinical Material and Methods of Study. In Guadalajara typhus is a frequent cause of fever and is part of an endemic triad including brucellosis and typhoid fever. Official statistics are lacking, but an approximation of the local prevalence of typhus is supplied by the study of Ruiz-Sanchez and his associates² who found positive Weil-Felix agglutinations in 11.1 per cent of 704 specimens of serum submitted for other serologic testing. These investigators considered as positive only those tests in which agglutination occurred in a dilution of 1:50 or higher. With due consideration for the fact that the Weil-Felix test may remain positive for many months after a typhus infection, these data indicate that the disease is widespread in the

region. Murine typhus is the variety which occurs most frequently³ and the clinical manifestations of the Guadalajara disease are identical with those seen in the murine typhus of other localities.

The characteristic findings in the typhus infections studied included: high fever, headache, a spotted rash in the first week of illness, splenomegaly and various types of gastrointestinal disturbances. Leukopenia and relative bradycardia are not uncommon so that in this locality it is virtually impossible to differentiate the early stages of typhus from the much more prevalent typhoid fever. Prostration is usually less severe in the typhus infections, however, a distinction which is occasionally of value. Complications of the typhus are not described and the case fatality rate is extremely low. All of the ten cases treated in Mexico clinically resembled murine typhus. The New York Hospital case was exposed to the rickettsia of endemic (murine) typhus in a research laboratory and also clinically conformed to the picture of the Mexican cases.

The diagnosis of typhus was established in all ten of the patients treated in Mexico by demonstration of a significant rise in agglutination titer in the Weil-Felix reaction. The final titer was as low as 1:160 in only one of these cases while in the others the titers ranged from 1:640 to 1:3200. These results are presented in Table I arranged according to the day of the disease.

The only other specific diagnostic procedure obtained was the complement fixation test.*

* These tests were obtained through the courtesy of Doctor Herald Cox, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

† One of these patients was treated at the New York Hospital during the period of the Mexican investigation.

* From the Institute for the Experimental Study of Infections of the University of Guadalajara, Jalisco, Mexico, and the Department of Medicine of the New York Hospital-Cornell University Medical College, New York, N. Y. The study was aided in part by grants from: The Division of Research Grants and Fellowships of the National Institutes of Health, U.S. Public Health Service; the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York; and Charles Pfizer and Company, Brooklyn, New York.

† National Institutes of Health, U.S. Public Health Service, Postdoctorate Research Fellow.

The results of these tests are shown in Table II and are also arranged according to the day of disease. The titers observed indicate the presence of rickettsial antibodies in the majority of the cases, and in four the reaction was slightly greater against the rickettsiae of epidemic

last seven patients treated in the series, also adults, received 175 to 200 mg. per Kg. per day in equally divided doses at three-hour intervals. One of the patients received therapy for twenty-four hours only, four for thirty-six hours and two for a total of forty-eight hours. (Table III.)

TABLE I
WEIL-FELIX REACTION* ACCORDING TO DAY OF DISEASE

Patient	Day of Disease†									
	4	6	8	10	12	14	16	18	20	22
R. Gon.....	0	0	1:320	1:800					
W. Ro.....	1:640	1:3200	1:3200
P. De.....	0	1:160	..	1:160			
F. Mo. (NYH).....	0	0					
L. Av.....	1:40	1:80	..	1:320	1:640		
P. Os.....	1:320	1:640					
R. Gom.....	..	1:640	1:640							
G. He.....	1:80	1:160	1:640					
E. Al.....	..	0	1:640						
A. Nu.....	..	1:80	1:320	1:1920					
T. Go.....	1:640	1:1920					

* *Proteus* OX 19 antigen.
† Odd days reported on next day.

typhus. The patient treated in the New York Hospital had several Weil-Felix tests with no agglutination, but a complement fixation test was reported in which titers of 1:256 or greater against both endemic and murine antigens were observed. Unfortunately, however, it was not possible in any of the cases to obtain rickettsial agglutination tests in order to determine whether the individual infections treated were murine or epidemic typhus. For the reasons presented above it is believed that all of the group were infected with the murine variety.

Examinations of the urine and determinations of the total leukocyte and erythrocyte counts and the concentration of hemoglobin were made before and after therapy. The results were consistent with the diagnosis of typhus and revealed no evidence of aureomycin toxicity.

Aureomycin was administered orally in divided doses in 100 and 250 mg. capsules. The first three patients treated were adults who received 6 Gm. the first day and 4 Gm. daily for five additional days (approximately 53 to 89 mg. per Kg. per day). The New York Hospital patient received 6 Gm. daily for three days and 4 Gm. daily for the four succeeding days (approximately 90 mg. per Kg. per day). The

No determinations of the concentrations of aureomycin in the blood were made in any of the cases.

Antimicrobial therapy was started on or before the eighth day of the disease in eight patients, and on the tenth, twelfth and sixteenth day in the remainder. A summary of the data concerning dosage and clinical course is presented in Table III.

RESULTS

In every instance the institution of therapy was followed by a remarkable improvement in all of the signs and symptoms of the typhus. The change was clearly evident in the first twenty-four hours in all the patients although in four the fever persisted longer and in one case for as long as seventy-two hours. Even in these four patients, however, the temperature was never elevated to more than 38°c. after the first day of chemotherapy. Headache and gastrointestinal symptoms disappeared overnight and the rash, when present at the start of therapy, faded completely in two to three

days. The duration of fever after therapy may be seen in Table III and Figure 1.

Other than occasional vomiting of the medication no significant toxic effects were observed in any of these patients. In no instance was the vomiting of sufficient severity to cause therapy to be discontinued.

between three and six months following the treatment with aureomycin.

BRUCELLOSIS

Clinical Material and Methods of Study. Five young adults with brucellosis were treated with aureomycin. Four were acutely febrile at the

TABLE II
COMPLEMENT FIXATION* ACCORDING TO DAY OF DISEASE

Patient	Antigen	Day after Onset								
		6	8	10	12	14	16	18	20	22
R. Gon.	Epidemic	1:32†	..	1:32						
	Murine	1:16	..	1:16						
	Anti-comp.	1:8	..	1:8						
W. Ro.	Epidemic	1:32	1:64
	Murine	1:16	1:32
	Anti-comp.	1:4	1:8
P. De.	Epidemic	1:16	..	1:32		
	Murine	1:8	..	1:16		
	Anti-comp.	1:4		
F. Mo. (NYH)	Epidemic	1:256†		
	Murine	1:256†		
L. Av.	Epidemic	0				
	Murine	0				
P. Os.	Epidemic	1:16				
	Murine	0				
R. Gom.	Epidemic	not tested								
	Murine	not tested								
G. He.	Epidemic	0					
	Murine	0					
E. Al.	Epidemic	not tested								
	Murine	not tested								
A. Nu.	Epidemic	not tested								
	Murine	not tested								
T. Go.	Epidemic	0					
	Murine	1:4					

* The writers are indebted to Dr. Herald Cox, Lederle Laboratories Division of American Cyanamid Co., for the performance of these tests.

† Each value represents titers interpreted as 3 + or greater.

‡ Or higher.

Relapse of the infection has not been observed. The subsequent course of the group has been followed for periods ranging

start of therapy and one was afebrile with a chronic form of the disease. In the febrile group the diagnosis was established by the demonstra-

tion of bacteremia in two cases and by significant rise in antibody titer in the two others. The presence of the chronic infection was established by means of serum agglutination tests and by a blood culture obtained in an outside laboratory ten days before the start of treatment.

TABLE III
FEBRILE COURSE AFTER START OF AUREOMYCIN THERAPY
IN TYPHUS

Patient	Day after Onset Treatment Begun	Dosage Regimen		Hours Febrile* after Therapy
		Duration of Treatment	mg./Kg./day	
R. Gon.....	4	6 days	53	48
W. Ro.....	16	6 "	57	36
P. De.....	6	6 "	89	24
F. Mo. (NYH)	10	7 "	90	72
L. Av.....	8	48 hours	200	24
P. Os.....	12	48 "	200	24
R. Gom.....	7	36 "	175	36
G. He.....	8	36 "	200	24
E. Al.....	6	36 "	200	48
A. Nu.....	6	33 "	177	48
T. Go.....	8	24 "	200	24

* 37.5°C. or greater.

The results of the laboratory tests obtained in these patients are presented in Table iv. Examinations of the blood and urine before and after therapy disclosed no evidences of toxicity or findings inconsistent with the diagnosis of brucellosis.

All of the four patients with acute infections presented the characteristic clinical manifestations of brucellosis. In addition, one patient (T. F.) had definite signs and symptoms of

meningeal involvement. The four acutely ill patients had been febrile for nine, twenty-six, sixty and ninety-five days, respectively, before treatment. The patient with chronic infection had been ill for two years and exhibited symptoms of malaise, general poor nutritional state,

TABLE IV
LABORATORY DIAGNOSIS OF BRUCELLOSIS

Patient	Serum Agglutination	Blood Culture
	(range)	
J. G.	1:80 to 1:640	+†
T. F.*	1:640 to 1:640	+
A. C.†	1:80 to 1:320	0
C. M.	1:180	+
G. V.	1:500	+

* This strain reacted as *B. melitensis* in the dye differentiation and sulfide production tests.

† Following first serum agglutination reported, this patient received brucella antigen as therapy.

‡ During relapse.

joint pains and occasional episodes of evening temperature elevation.

Aureomycin was employed in a manner similar to that used in the treatment of murine typhus. In general, the regimen consisted of 6 Gm. of drug the first day in divided doses and 4 Gm. daily thereafter for an additional five days. One patient (C. M.) received 9.5 Gm. daily for seven days and the patient with meningeal involvement received treatment for only three and one-half days before leaving the hospital against advice. (Table v.)

RESULTS

The results following therapy in the febrile cases were striking. In each case

TABLE V
CLINICAL COURSE IN TREATED BRUCELLOSIS

Patient	Days Ill at Start of Treatment	Temperature*	Immediate Clinical Result	Days Febrile after Start of Treatment	Follow-up
J. G.	9	39.0	Marked improvement	3	Relapse after 42 days
T. F.	26	39.0	Marked improvement	4	Asymptomatic—3 months
A. C.	95	39.3	Marked improvement	4	Asymptomatic—4½ months
C. M.	60	38.5	Marked improvement	4	Relapse after 15 days
G. V.	2 years	Normal	No change	..	No change

* Highest temperature on the day before therapy was started.

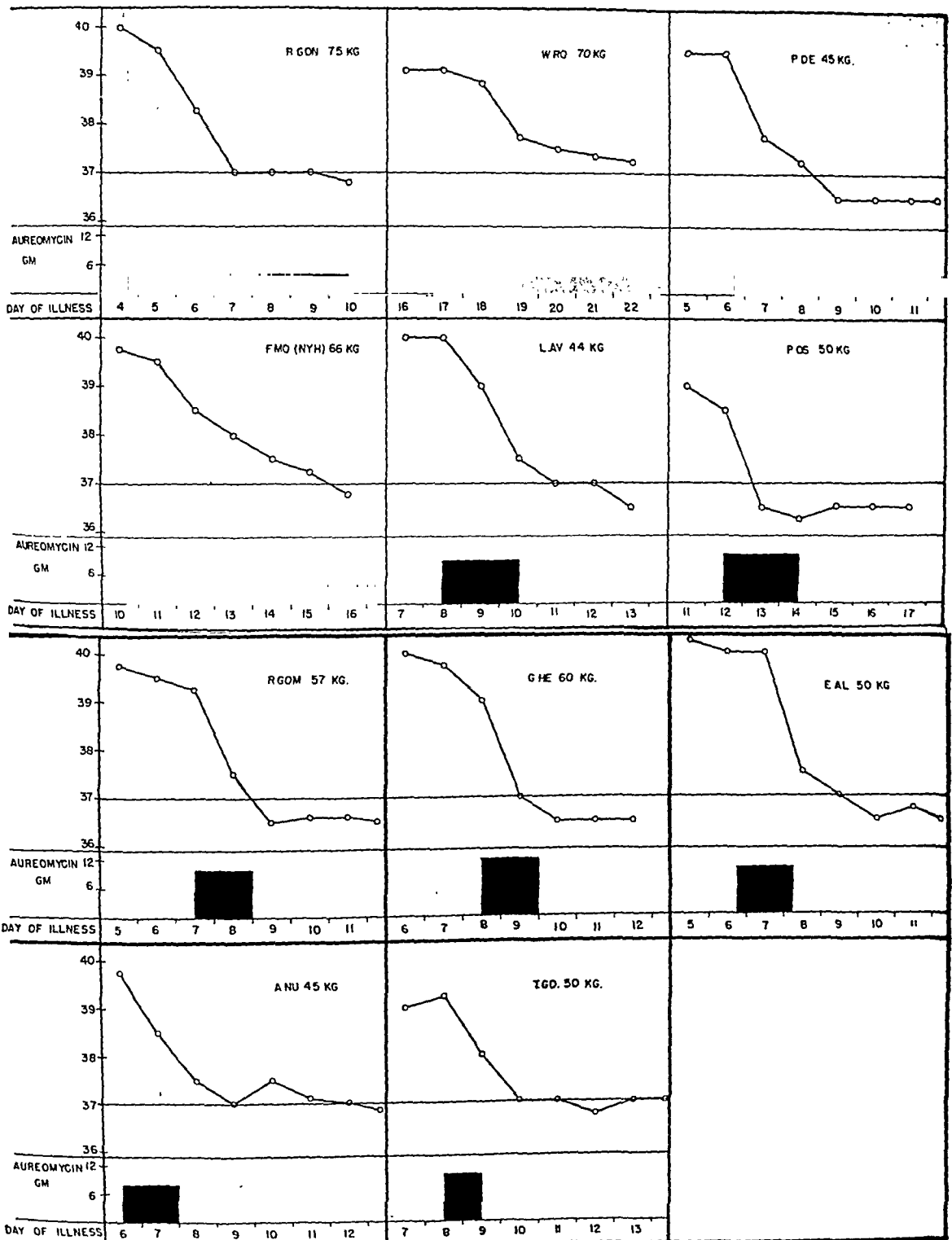


Fig. 1. Maximal daily temperatures after aureomycin treatment in typhus fever, showing immediate and uniform return of the temperature to normal.

temperatures which had reached a daily high of 38.5°C. or more prior to treatment promptly fell and were within the normal range within four days. Improvement in the other clinical manifestations was also rapid, with loss of joint pains and malaise,

were also present on the left. All sensory functions appeared to be normal. The spleen was not palpable and the remainder of the examination, including fluoroscopy of the chest, revealed no significant abnormal findings. The presence of brucella

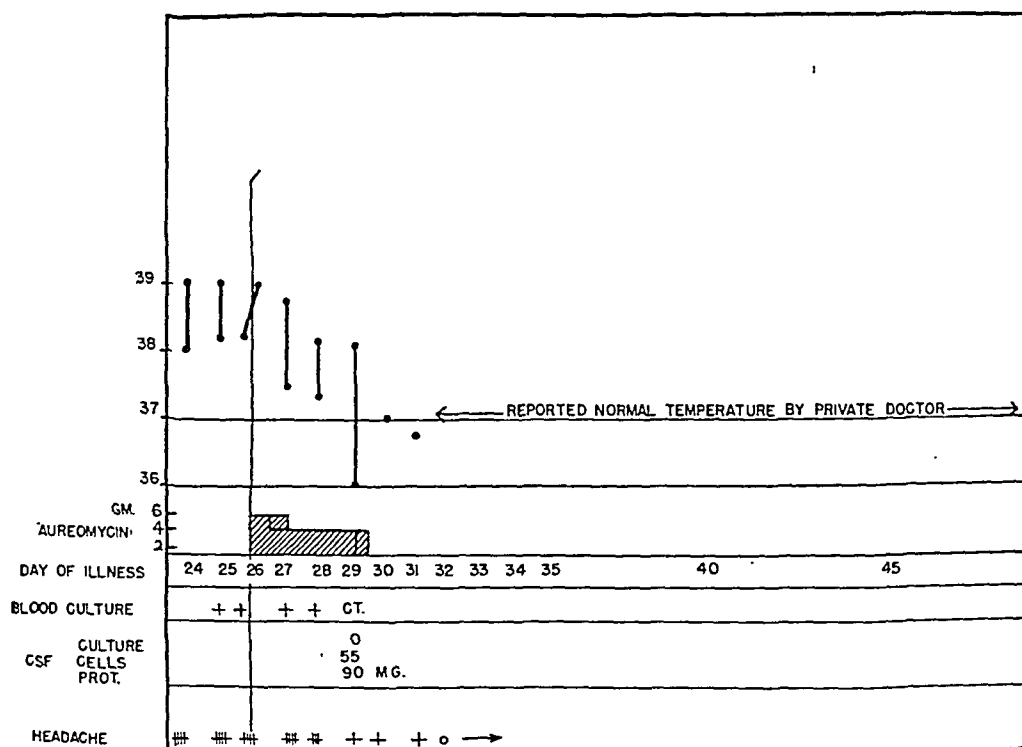


FIG. 2. Chart of patient T. F., who had acute meningo-encephalitic brucellosis and who was treated with aureomycin, showing improvement after treatment with return of the temperature to normal.

and return of appetite and general well being within a few days of the start of antimicrobial therapy.

The most impressive evidence of antimicrobial effect observed was the course of the infection in the patient (T. F.) with acute meningo-encephalitis. (Fig. 2.) The patient was a woman of twenty-four years who had fever and joint pains for one month before normal termination of a pregnancy. Immediately after delivery her condition became worse, with high fever, severe frontal headache, vomiting, generalized aches and pains and stiffness of the neck. Physical examination seven days postpartum revealed moderately severe bilateral papilledema and nuchal rigidity. Hyperreflexia was present and most marked on the left. Hoffman's and Babinski's signs

bacteremia was repeatedly demonstrated. Examination of the cerebrospinal fluid revealed a total protein concentration of 90 mg. per 100 cc. and 55 cells (all mononuclear) per cu. mm. Culture of the fluid in a liver infusion medium and in trypticase soy broth revealed no growth.

As may be seen in Figure 2, defervescence started soon after the first administration of aureomycin and by the end of a seventy-two hour period of therapy the patient was completely afebrile. Moreover, the disappearance of fever was accompanied by a marked diminution of the evidences of central nervous system involvement. The nuchal rigidity and the abnormal reflex responses disappeared promptly and the papilledema was greatly diminished when the patient left the hospital on the fourth

day of treatment. The intensity of the headache steadily decreased and this symptom disappeared entirely during the first week at home. The patient has remained completely asymptomatic during the four months since the cessation of antimicrobial therapy.

preceding antimicrobial therapy and conceivably was related to it. With the disappearance of fever the patient improved rapidly although it was several weeks before she felt entirely well and asymptomatic. The remission of her disease has been maintained

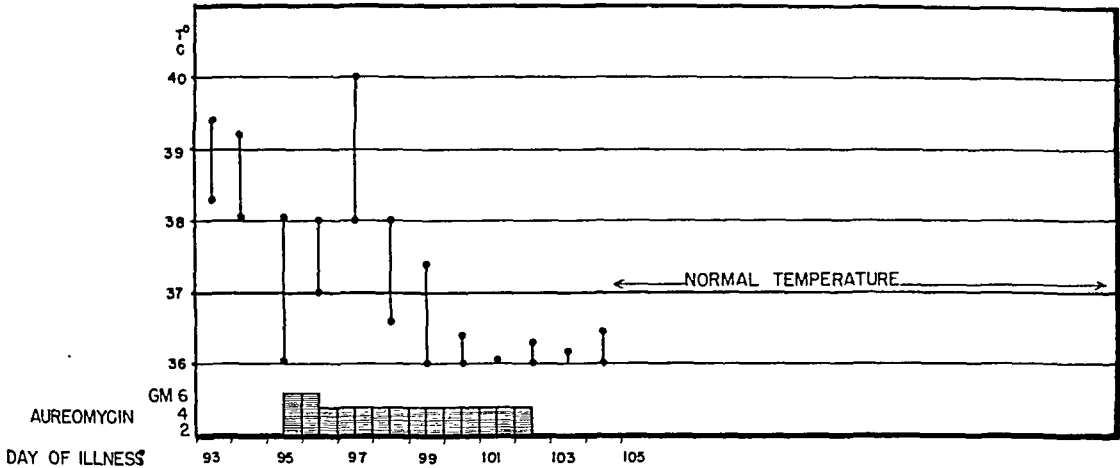


FIG. 3. Chart of patient A. C., who had acute brucellosis and who was treated with aureomycin, showing abrupt rise in temperature at the forty-eighth hour of treatment followed by complete clinical remission.

It should be noted that despite the immediate clinical improvement the bacteremia persisted for at least forty-eight hours after aureomycin therapy was started.

A phenomenon of possible significance was noted during the early period of chemotherapy of a twenty year old female (A. C.) who had been acutely ill with brucellosis for ninety-five days. When aureomycin was instituted, her principal symptoms consisted of weakness, weight loss, malaise, joint pains, night sweats, dizzy spells and tachycardia. Her temperature ranged daily from 38° to 40°C. throughout the pretreatment period except for a few three- to four-day afebrile intervals.

As may be seen in Figure 3, approximately thirty-six hours after the start of treatment the patient experienced an abrupt elevation of temperature to 40°C. accompanied by a shaking chill. The temperature remained above 39.5°C. for a period of approximately twelve hours and then fell during the ensuing twenty-four hours to the normal range where it remained thereafter. This episode was in contrast to the course of her infection in the days immediately

during a follow-up period of approximately five months.

The third patient was a twenty-one year old male (J. G.) who was started on aureomycin therapy after only nine days of illness. Defervescence occurred during the first seventy-two hours of antimicrobial therapy and was accompanied by complete disappearance of all symptoms. After an afebrile period of forty-two days, however, fever and arthralgia recurred and was accompanied by bacteremia due to brucella. The reinstitution of aureomycin was again followed by a remission of all signs of the infection and the patient has been entirely well during the subsequent two and one-half months.

The fourth patient (C. M.) received a larger dose of drug than the first three cases. Her clinical response, however, closely resembled that of J. G. except that ninety-six hours were required for defervescence. Fifteen days following cessation of therapy a relapse occurred, with fever, bacteremia and a return of symptoms. Because the patient moved from the city, retreatment was not possible.

The patient with chronic brucellosis was afebrile at the start of therapy and showed no alteration of symptoms attributable to therapy. Pain and stiffness in both knees persisted after treatment. A feeling of malaise with poor appetite was present during the follow-up interval of three weeks. As cultures were negative at the time treatment was begun, there was no satisfactory means for the evaluation of therapy. It is of interest, however, that the patient experienced absolutely no symptomatic improvement in contrast to the course of events after therapy in the patients with acute infections.

COMMENT

Typhus. In the eleven patients with typhus the uniformity with which all clinical manifestations of the infection rapidly disappeared after the start of aureomycin therapy affords evidence that the observed remissions were drug-induced. Recovery by "crisis" may occur in typhus fever but is unusual.⁴ In contrast, in the aureomycin treated patients recovery by "crisis" occurred uniformly. The average duration of fever after the start of therapy was only 1.7 days, and this appeared not to vary greatly whether the treatment was started on the fourth, seventh, eighth, twelfth or sixteenth day of illness. Because of the variable time at which treatment was started no precise comparison can be made with the natural course of the untreated disease.

In Guadalajara untreated typhus usually runs a febrile course for approximately two weeks³ but fever may persist for twenty or more days. In 180 cases of murine typhus studied at Charity Hospital, New Orleans, by Stuart and Pullen⁵ the average febrile period was 15.6 days, while in Woodward's careful study of the length of the febrile period in fourteen cases of murine typhus in North Africa⁴ the average febrile period was twelve days.

From the above data it appears that the administration of aureomycin exerted a prompt and impressive effect upon the

course of infection in the eleven patients with typhus. It is also impressive that no relapses were observed despite the fact that in seven patients the total period of antimicrobial therapy was limited to only one or two days. Although these short periods of therapy were apparently effective, they do not necessarily represent the ideal dosage regimen. The latter can be determined only by the treatment of a much larger series of patients.

Payne,⁶ Smadel,^{7,9} Woodward⁸ and their respective associates have demonstrated that chloromycetin exerts a striking effect upon the course of several varieties of typhus and spotted fever. Whether either chloromycetin or aureomycin is materially superior to the other in terms of antirickettsial effectiveness must await the results of direct comparative studies. On the basis of the evidence available at present, however, it appears that both drugs are powerful antirickettsial agents which exert a considerably greater effect than para-aminobenzoic acid, the most satisfactory of the antirickettsial agents hitherto available.⁹

Brucellosis. Remissions of the acute manifestations of brucellosis may occur with such abruptness and with sufficient frequency that it is difficult to evaluate antimicrobial agents in the treatment of this infection. Consequently the fact that the four patients in the present study all experienced a complete remission of their acute disease soon after the start of aureomycin therapy can be considered only as suggestive of a drug effect. The course of events in the patient with meningo-encephalitis and bacteremia, however, affords much more impressive evidence of drug effect. Meningo-encephalitis occurs infrequently in brucellosis but represents a serious complication. Of two cases reported by Huddleson¹¹ one died after a protracted illness and the other continued to present abnormal neurologic signs for more than six months before gradual improvement was first observed. In contrast, in the aureomycin treated patient with meningo-encephalitis, deservescence and dramatic symptomatic improvement ap-

peared within forty-eight hours of the start of chemotherapy and complete recovery occurred during the subsequent week. It is believed that such a rapid recovery from acute meningo-encephalitis with bacteremia would have been most unlikely in the natural course of the infection and presumably represents an effect attributable to the aureomycin.

As noted above, in one patient (A. C., Fig. 3) the onset of defervescence was immediately preceded by an intensification of the evidences of infection manifested by a chill, a sudden elevation in temperature and tachycardia with bothersome cardiac palpitation. These symptoms appeared approximately forty-eight hours after the start of aureomycin therapy, were of only moderate severity and may well have merely represented daily variations in the intensity of the infection. The incident is worthy of mention, however, because of the observation of Spink and Castaneda and their associates¹² that certain of their patients with acute brucellosis experienced rather alarming intensification of the infection during the first day of aureomycin therapy. In the other three patients with acute brucellosis in the present series (two of whom were bacteremic) the onset of defervescence was not preceded by intensification of the illness.

As with the typhus patients, considerably more experience with the aureomycin treatment of brucellosis must be acquired before the most satisfactory dosage regimens are defined. The patient with meningo-encephalitis experienced a remission which has been sustained for four months after only three and one-half days of antimicrobial therapy. Nevertheless, the appearance of a febrile relapse in two patients fifteen and forty-two days after a one-week period of aureomycin therapy indicates that a longer total period of therapy will probably prove to be advisable.

SUMMARY

The administration of aureomycin* to eleven patients with typhus (presumably

* The aureomycin used in this investigation was sup-

plied through the courtesy of Doctor Benjamin Carey, Director, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

murine) was followed in every instance by prompt defervescence and complete recovery. No instances of relapse were observed despite the fact that in seven cases the total period of antimicrobial therapy was limited to forty-eight hours or less.

In four patients with acute brucellosis, one of whom had meningo-encephalitis, a similar prompt disappearance of the manifestations of the infection occurred soon after the start of aureomycin therapy.

ADDENDUM

Since this material was submitted for publication, an additional eight patients with typhus fever have been successfully treated with aureomycin. Seven of these patients were treated with oral dosages ranging from 100 to 160 mg. per Kg. per day, for intervals of thirty-six to forty-eight hours. These patients all showed rapid improvement after therapy in every way as satisfactory as that described for the previous patients. Five of these patients had continuously normal temperatures within thirty hours after starting therapy while the two remaining individuals, although greatly improved, showed slight elevations of temperature on the third day after starting treatment. In one of these cases this slight rise in temperature was associated with profuse epistaxis which responded to local treatment. Convalescence was otherwise uneventful.

One patient in the eighth day of her illness received aureomycin intravenously. She was given doses of 200 mg. at approximate eight-hour intervals during the first day and at twelve-hour intervals during the second day. Improvement was rapid so that by the time the last dose was administered she was essentially asymptomatic and permanently afebrile. Convalescence was entirely uneventful and there was no local or systemic evidence of reaction to therapy.

Other patients were treated with lower oral dosages in an attempt to discover a

subeffective dose. One such patient, treated with 25 mg. per Kg. per day for thirty-six hours, showed appreciably less benefit from therapy than those receiving larger doses. From these observations it appears that the lowest fully effective dose may lie somewhere between 50 and 100 mg. per Kg. per day for a short interval of therapy.

REFERENCES

1. KNIGHT, VERNON, RUIZ-SANCHEZ, FRANCISCO, SHULTZ, SELMA, RUIZ-SANCHEZ, AMADO and McDERMOTT, WALSH. The antimicrobial therapy of typhoid fever. (To be published.)
2. RUIZ-SANCHEZ, FRANCISCO, PONCE DE LEON, ESTELA and OROZCO, GUILLERMO. La frecuencia del tifo en Guadalajara. *Medicina, Mexico*, 26: 2, 1946.
3. RUIZ-SANCHEZ, FRANCISCO. Estudios sobre el tifo de Guadalajara. *Medicina, Mexico*, 24: 363, 1944.
4. WOODWARD, THEODORE E. Endemic (murine) typhus fever: symptomatology. The Rickettsial Diseases of Man. P. 169. Washington, D. C., 1946. Am. Assoc. Adv. Sc.
5. STUART, BYRON M. and PULLEN, ROSCOE L. Endemic (murine) typhus fever: clinical observations of 180 cases. *Ann. Int. Med.*, 23: 520, 1945.
6. PAYNE, EUGENE H., KNAUDT, JOSE A. and PALACIOS, SYLVIA. Treatment of epidemic typhus with chloromycetin. *J. Trop. Med. & Hyg.*, 51: 68, 1948.
7. SMADEL, JOSEPH E., LEON, ALBERT P., LEY, HERBERT L. and VARELLA, GERARDO. Chloromycetin in the treatment of patients with typhus fever. *Proc. Soc. Exper. Biol. & Med.*, 68: 12, 1948.
8. PINCOFFS, M. C., GUY, ERNEST G., LISTER, LEONARD M., WOODWARD, THEODORE E. and SMADEL, JOSEPH E. The treatment of Rocky Mountain spotted fever with chloromycetin. *Ann. Int. Med.*, 29: 656, 1948.
9. SMADEL, J. E., WOODWARD, T. E., LEY, H. L., JR., PHILIP, C. B., TRAUB, R., LEWTHWAITE, R. and SAVOOR, S. R. Chloromycetin in the treatment of scrub-typhus (read before Internat. Cong. Trop. Dis., Washington, D. C., May 11, 1948). *Science* (In press).
10. SNYDER, JOHN C. The treatment of the rickettsial diseases of man. The Rickettsial Diseases of Man. P. 169. Washington, D. C., 1946. Am. Assoc. Adv. Sc.
11. HUDDLESON, I. FOREST. Brucellosis in Man and Animals. New York, Pp. 285, 293. 1939. The Commonwealth Fund.
12. SPINK, WESLEY W., BRAUDE, ABRAHAM I., RUIZ CASTANEDA, M. and SYLVIA GOYTIA, ROBERTO. Aureomycin therapy in human brucellosis due to *Brucella melitensis*. *J. A. M. A.*, 138: 1145, 1948.

Effect of Streptomycin Therapy on the Bacterial Flora of the Throat*

C. PHILLIP MILLER, M.D. and MARJORIE BOHNHOFF, S.B.

Chicago, Illinois

SEVERAL investigators have reported that bacteria can develop resistance to streptomycin rapidly and to a high degree either in artificial culture media or during streptomycin treatment of an infectious process in man. This sudden development of resistance is presumed to result from the appearance of streptomycin-resistant variants which arise by mutation in the bacterial population.

With one exception,¹ the clinical reports seem to indicate that the streptomycin-resistant strains thus far recovered are analogous to the type A variant described by the authors and so designated to distinguish them from a second variant designated type B.² Both types have in common the ability to grow in high concentrations of streptomycin but are distinguished by the fact that the type A variant can multiply in the absence of streptomycin whereas type B requires streptomycin for its growth *in vitro* and *in vivo*.

Variants of both types have been found to arise in cultures of sensitive bacteria during their initial exposure to streptomycin when heavy seedings are spread on agar plates containing appropriate concentrations of the drug. They have been isolated from all of eighteen strains of meningococcus and also from a number of other bacterial species including *Aerobacter aerogenes*, *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas pyocyanea*, *Salmonella* and *Staphylococci*.³ These findings have been confirmed by Kushnick, Randles, Gray and Birkeland,⁴ by Paine and Finland,⁵ by Yegian and Budd⁶ and by Rake.⁷

The question naturally arises whether the

streptomycin-dependent variants occur in nature or only under the artificial conditions of laboratory experimentation. A search for type B variants was therefore made in animals and in patients undergoing treatment with streptomycin.

ANIMAL EXPERIMENTS

Streptomycin* in large doses was administered to normal mice and rabbits for periods up to three weeks. The mice received 2,000 micrograms twice a day subcutaneously or orally and the rabbits 50,000 micrograms once a day intravenously. All the animals remained healthy. From time to time an animal was sacrificed and cultures were made of the heart's blood, pharynx, large bowel and spleen onto media containing 400 micrograms of streptomycin per cc.

RESULTS

Streptomycin-resistant organisms were plentiful in the large bowel of both normal and treated mice and rabbits. During the second week of treatment streptomycin-dependent organisms began to appear. Their maximal incidence was estimated to be about 10 per cent of the micro-organisms which grew on streptomycin-containing media. At the beginning of the experiment pharyngeal cultures of the mice were negative on streptomycin media but became

* Preparations of streptomycin were supplied by the Antibiotics Study Section of the National Institute of Health, U. S. Public Health Service; the Division of Penicillin Control and Immunology, Food and Drug Administration; Abbott Laboratories; Commercial Solvents Corporation; Eli Lilly & Company; Merck & Company; Chas. Pfizer & Company; E. R. Squibb & Son and Upjohn Company.

* From the Department of Medicine, University of Chicago, Chicago, Ill. This investigation was undertaken and supported jointly by the U. S. Navy, Office of Naval Research, and the University of Chicago.

positive on the eleventh day and continued so until the end of the experiment. The cultures always contained some streptomycin-dependent micro-organisms although ordinary streptomycin-resistant organisms predominated.

Hearts' blood and spleen cultures remained negative throughout the experiment. The varieties of micro-organisms encountered in the pharynx and bowel differed in only one respect from those which make up the normal flora of these sites. There was an unusually high incidence of yeasts which constituted a large proportion of the streptomycin-dependent variants.

CULTURES ON PATIENTS

Cultures on streptomycin-containing media⁸ were made of the throats of patients undergoing treatment with streptomycin. The posterior pharyngeal wall was swabbed with two applicators. One swab was used to inoculate a blood (5 per cent defibrinated sheep's blood) agar plate containing 200 micrograms of streptomycin per cc. and the other a plate containing 400 micrograms of streptomycin per cc. The plates were incubated and examined at the end of twenty-four, forty-eight and seventy-two hours at which times the numbers of colonies were recorded. A culture was considered positive when five or more colonies were visible at forty-eight hours. The amount of growth appearing on the two plates containing 200 and 400 micrograms per cc. was approximately the same.

Representative cultures were studied in detail in order to determine whether the colonies were type A or type B variants. Single colonies were picked and subcultured onto both ordinary blood agar and onto media containing 100 micrograms of streptomycin per cc. Smears were stained by Gram's method and examined microscopically.

Additional cultures were taken from a number of throats which had been found to yield heavy growth in order to estimate what proportion of the total bacterial population was streptomycin-resistant or dependent. The throat was swabbed in the usual way and the swab rinsed in 2 cc. of broth from which a series of two-fold dilutions was made. Equivalent inocula were cultured in duplicate onto ordinary blood agar and blood agar containing 200 micrograms of streptomycin

per cc. and spread by means of glass beads as described in an earlier publication.²

The first series of cultures was made on patients in the Albert Merritt Billings Hospital of the University of Chicago. They included patients receiving streptomycin for the treatment of tuberculosis, ulcerative colitis, brucellosis or urinary tract infections and surgical patients being treated with streptomycin as a prophylactic measure. Those with pulmonary tuberculosis had been treated with streptomycin for a number of weeks before the first cultures were made. Many of the others, however, were followed from the time streptomycin therapy was begun and cultures were made daily until they became strongly positive.

The patients were given streptomycin intramuscularly in doses of 1.0 to 3.0 Gm. per day except those with colitis who took 4 Gm. per day by mouth. Some of the patients received penicillin and/or one of the sulfonamide drugs as well as streptomycin.

Control cultures were made on 157 members of the staff, students, laboratory and clerical personnel; on ninety-nine nurses and ward attendants and on seventy patients who were not receiving streptomycin.

In order to supplement our series of cultures on streptomycin-treated patients a survey was made of 114 patients undergoing streptomycin therapy in the Chicago Municipal Tuberculosis Sanitarium.* With eight exceptions all of the patients were receiving only 0.5 Gm. a day or 0.75 Gm. a day if their weight exceeded 70 Kg. The eight exceptions were patients treated with 1.0, 1.5 or 2.0 Gm. per day, and in the final tabulation they are included in the Billings series of patients. The patients in the M.T.S. series had been treated with streptomycin from three days to forty-five weeks. The cultures were taken as just described except that a single swab was used to inoculate a single plate containing 200 micrograms of streptomycin per cc.

RESULTS

Billings Series. The throat cultures of all but one of sixty-one patients in this series became positive. Cultures of fifty-five of them showed very heavy growth on streptomycin-containing media, indicating the presence of large numbers of streptomycin-

* The authors are indebted to Dr. George C. Turner, Superintendent of The Chicago Municipal Tuberculosis Sanitarium, for the opportunity to make these cultures.

resistant micro-organisms in the pharynx. Figure 1 presents the results of individual cultures on twenty-four patients who were followed from the beginning of streptomycin therapy or shortly thereafter. It will be seen that all of these cultures became positive by the thirteenth day.

taken from the third to the eighth day of streptomycin therapy. The bacteria on these plates included a *Staphylococcus albus* and a hemolytic *Staphylococcus aureus*.

We do not know when resistant bacteria appeared in the throats of the other thirty-

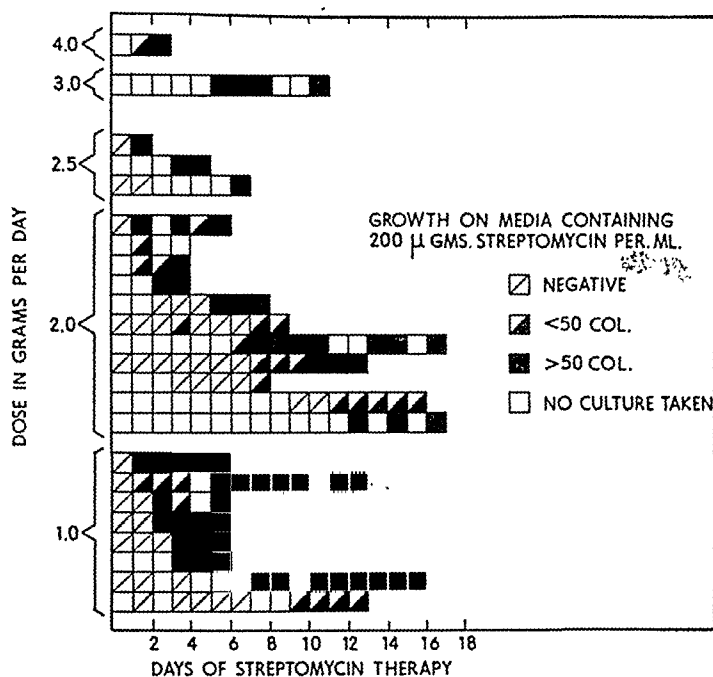


FIG. 1. Results of serial throat cultures in twenty-four patients receiving streptomycin.

Figure 2 illustrates the rate at which streptomycin-resistant bacteria appear in the throats of such patients by showing a series of daily cultures taken on two typical patients. Patient PG was a seventeen-year old boy weighing 30 Kg. who received 1 Gm. of streptomycin per day for the treatment of tuberculosis of the lungs and lumbar spine. The throat cultures shown in the photographs were made daily on streptomycin agar from the beginning of therapy. The micro-organisms isolated from his cultures on streptomycin blood agar plates were *Micrococcus tetragenus* and a few yeasts. Patient BK was a twenty year old woman who was admitted for excision of a pilonidal cyst. She was given 2 Gm. of streptomycin per day and 300,000 units of penicillin procaine and 5 or 6 Gm. of sulfadiazine per day.

Figure 2 shows the results of cultures

seven patients in the Billings series because they had been receiving streptomycin for some time before the cultures were taken. It should be noted that all of the patients in this series received 1 Gm. or more of streptomycin per day. The results of cultures on these sixty-one patients can be seen in Figure 3.

The bacteria recovered from cultures on streptomycin media were for the most part representative of the ordinary flora of the normal human throat, i.e., staphylococci, green-forming streptococci, pneumococci, *Micrococcus tetragenus*, *Neisseriae* and some of the coliform group. The only unusual finding was a much higher incidence of yeasts or yeast-like fungi than is ordinarily encountered. These were not identified taxonomically. Colonies on blood agar and Sabouraud's medium resembled ordinary *Staphylococcus albus*. Most of

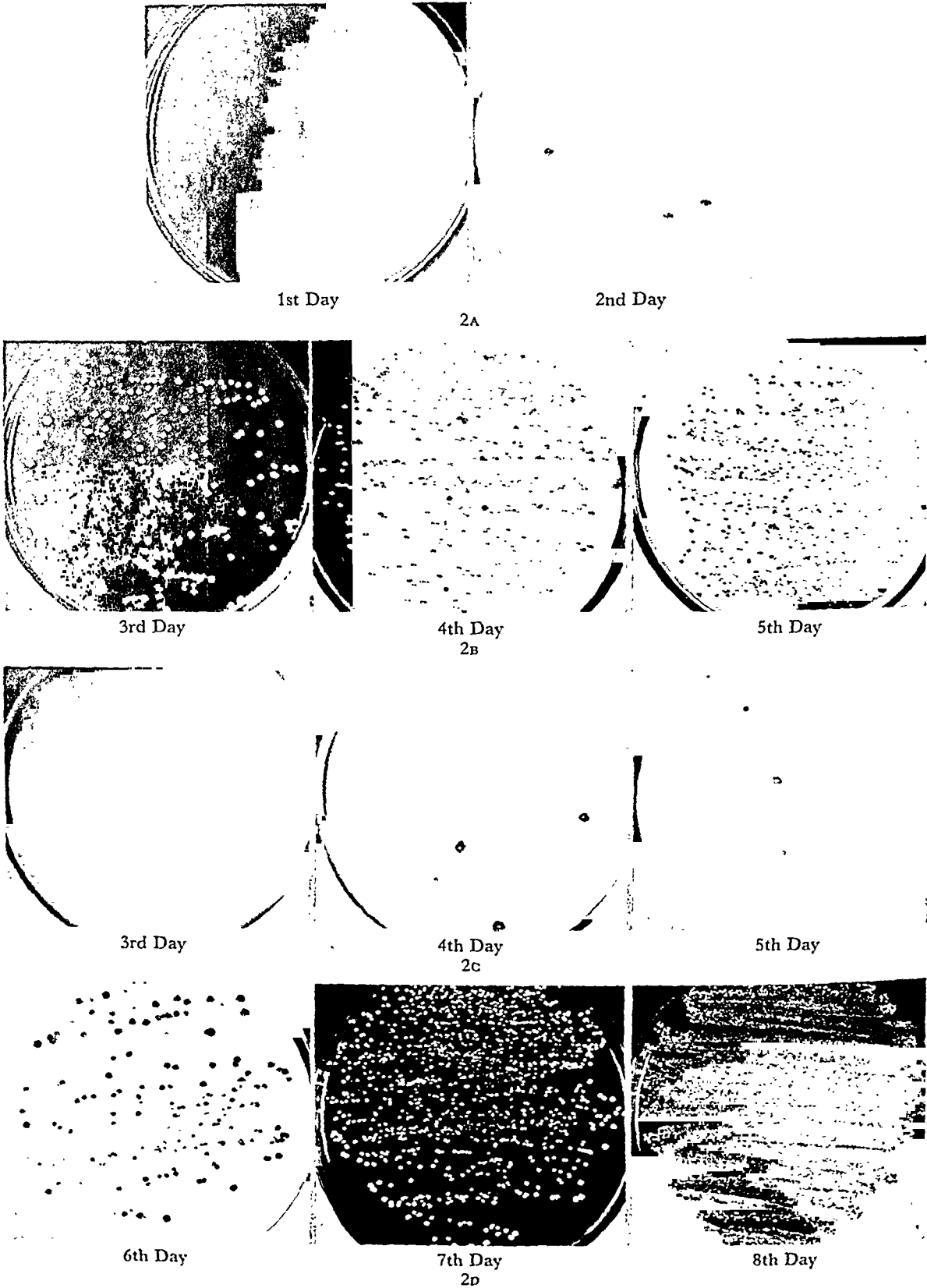


FIG. 2. Serial throat cultures in two patients receiving streptomycin. Numbers designate days of streptomycin therapy. A and B, patient P. G., c and D, patient B. K.

them produced no hyphae. Microscopically, the cells had the typical appearance of yeasts, large budding forms.

From the broth dilution cultures made to determine what proportion of the total bacterial population was streptomycin-re-

seven cultures containing some colonies of streptomycin-resistant organisms. (Fig. 3.) Three of these positive cultures consisted entirely of yeasts. Of the 157 members of the staff, student body, laboratory and clerical personnel, many of whom were cultured

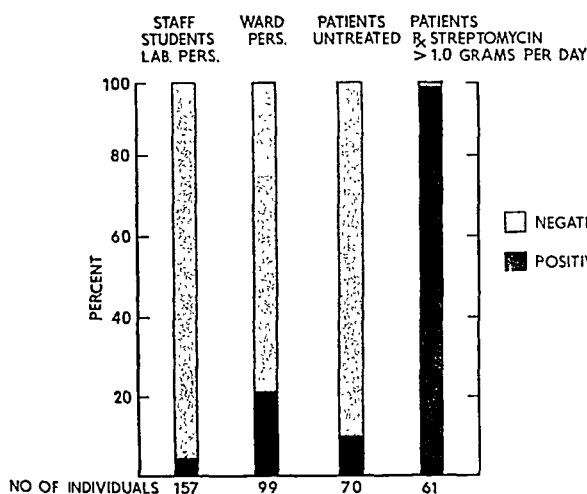


FIG. 3

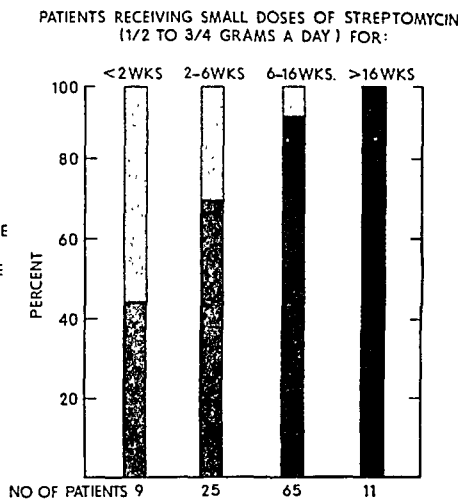


FIG. 4.

FIGS. 3 and 4. Results of throat cultures on streptomycin media (200 µgm. per ml.).

sistant or dependent it was found that ten to twenty times as many micro-organisms grew on the control media as on media containing 200 micrograms of streptomycin per cc.; in other words, 10 to 20 per cent of the micro-organisms swabbed from the throat were streptomycin-resistant or dependent. The concomitant administration of penicillin and/or a sulfonamide did not seem to retard the appearance of streptomycin-resistant or streptomycin-dependent organisms in the throat although it did reduce the variety of bacteria by eliminating most of the penicillin-sensitive and/or sulfonamide-sensitive organisms.

M.T.S. Series. A single culture was made on each of the patients in the second series who were receiving only 0.5 to 0.75 micrograms of streptomycin per day. The results of these cultures can be seen in Figure 4. It will be seen that a much smaller proportion of the cultures were positive during the first two weeks of therapy but that this proportion increased as treatment continued.

Among the seventy patients who were not receiving streptomycin there were

repeatedly, only six individuals had positive cultures, an incidence of 4 per cent. (Fig. 3.) Only one of these six patients had more than a few colonies per plate.

Among the ninety-nine members of the ward personnel, i.e., nurses and attendants, there were twenty-one positive cultures, an incidence of 21 per cent. (Fig. 3.) Four of these cultures showed heavy growth of streptomycin-resistant bacteria. It is interesting to note that these four cultures were from nurses who were at the time caring for patients receiving streptomycin.

Incidence of Streptomycin-dependent Bacteria. At least one culture on each of the patients in the Billings series was examined for streptomycin-dependent (type B) bacteria by picking eight or more colonies and subculturing onto streptomycin media (100 micrograms per cc.) and onto streptomycin-free media. Streptomycin-dependent bacteria were recovered in two-fifths of these patients as early as two days after treatment was started. The species encountered were green-forming streptococci, staphylococci, diphtheroids, gram-negative rods, *Neisseria catarrhalis* and *N. flava*. The twenty-one

positive cultures from nurses and ward attendants were similarly examined and streptomycin-dependent staphylococci were recovered from three, all of which were from nurses caring for patients receiving streptomycin.

COMMENT

It is evident from these data that streptomycin-resistant bacteria appeared among the normal flora in the throats of patients during the first week or two of streptomycin therapy if the dose was 1 Gm. or more per day. The time of their appearance seemed to be delayed in those patients who were receiving smaller doses (0.5 to 0.75 Gm. per day). Fig. 4.

Most of the resistant micro-organisms belonged to type A, but type B (streptomycin-dependent) bacteria were isolated from two-fifths of the patients in the Billings series. There is no reason to doubt that a more exhaustive study would have revealed the presence of greater numbers of dependent bacteria.

The micro-organisms recovered were all members of the species usually found in the normal human throat except that a greater number of yeasts was cultured than is ordinarily the case. In fact, a large proportion of the positive cultures in the control groups consisted only of yeasts or yeast-like fungi. These yeast-like micro-organisms were not identified. Most of them were presumed to be *Monilia* (*Candida* according to the newer terminology) because this is the yeast most commonly found in the human mouth.^{9,10} The high incidence in throat cultures on streptomycin media is a subject for further investigation.

It is of interest that penicillin and/or one of the sulfonamide drugs failed to prevent or even to delay the appearance of streptomycin-resistant organisms in the throat. Their administration did, however, eliminate the species most sensitive to those drugs. The change in flora was not as great as that described by Lipman, Coss and Boots¹¹ whose patients received much larger doses of penicillin for longer periods of time.

The highest incidence of streptomycin-resistant bacteria in untreated individuals occurred among nurses who were caring for patients undergoing treatment with streptomycin. This finding suggests that contact with these patients may have been responsible for the presence of streptomycin-resistant bacteria in their throats.

The unexpected finding of streptomycin-dependent bacteria in the throats of three nurses is as yet unexplained. The possibility has been considered that some substance present in the pharyngeal secretion of saliva of these individuals or a metabolic product of some microbial inhabitant may provide the necessary growth factor for streptomycin-dependent bacteria. We have thus far been unable to find any substance related to streptomycin or its derivatives which would replace streptomycin in the cultivation of the dependent bacteria *in vitro*.

SUMMARY

Specimens from the throats of patients receiving streptomycin were cultured onto streptomycin media in order to detect the presence of streptomycin-resistant and streptomycin-dependent bacteria. Streptomycin-resistant bacteria in large numbers were cultured from the throats of 98.4 per cent of sixty-one patients who were receiving 1 to 4 Gm. of streptomycin per day. They began to appear during the first thirteen days of treatment in the twenty-four patients who were followed from the beginning of streptomycin therapy.

Results of a single survey of another series of patients receiving small doses of streptomycin (0.5 to 0.75 Gm. per day) suggested that resistant flora appeared more slowly. These streptomycin-resistant bacteria all belonged to species normally inhabiting the human throat. Yeast-like forms (*Monilia*) were found in unusually high incidence. Streptomycin-dependent bacteria were found in two-fifths of the patients receiving large doses of streptomycin, i.e., 1 Gm. or more per day.

Streptomycin-resistant bacteria in small

numbers were recovered from only 4 per cent of 157 members of the hospital staff, student body and clerical personnel and from 10 per cent of untreated patients. The highest incidence of positive cultures in the control series, 21 per cent, occurred in the nursing and ward personnel. Strongly positive cultures were found in four nurses who were caring for patients receiving streptomycin.

Streptomycin-dependent micro-organisms were recovered from the pharynx and large bowel of mice and rabbits after one week of treatment with large doses of streptomycin.

REFERENCES

1. HALL, W. H. and SPINK, W. W. In vitro sensitivity of brucella to streptomycin; development of resistance during streptomycin treatment. *Proc. Soc. Exper. Biol. & Med.*, 64: 403-406, 1947.
2. MILLER, C. P. and BOHNHOFF, M. Two streptomycin resistant variants of meningococcus. *J. Bact.*, 54: 467-81, 1947.
3. Unpublished experiments by the authors.
4. KUSHNICK, T., RANGLES, C. I., GRAY, C. T. and BIRKELAND, J. M. Variants of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* requiring streptomycin. *Science*, 106: 587-588, 1947.
5. PAINE, T. F. and FINLAND, M. Streptomycin sensitive, dependent and resistant bacteria. *Science*, 107: 143-144, 1948.
6. YEGIAN, D. and BUDD, V. A variant of *Mycobacterium ranac* requiring streptomycin for growth. *J. Bact.*, 55: 459-461, 1948.
7. RAKE, G. Streptomycin as an essential nutrilit. *Proc. Soc. Exper. Biol. & Med.*, 67: 249-253, 1948.
8. MILLER, C. P. and BOHNHOFF, M. Studies on the action of penicillin. VI. Further observations on the development of penicillin resistance by meningococcus in vitro. *J. Infect. Dis.*, 81: 147-156, 1947.
9. TODD, R. L. Studies on yeast-like organisms isolated from the mouths and throats of normal persons. *Am. J. Hyg.*, 25: 212-220, 1937.
10. KNIGHTON, H. T. A study of monilia and other yeast-like organisms found in the oral cavity. *J. Dent. Research*, 18: 103-125, 1939.
11. LIPMAN, M. O., COSS, J. A., Jr. and BOOTS, R. H. Changes in the bacterial flora of the throat and intestinal tract during prolonged oral administration of penicillin. *Am. J. Med.*, 4: 702-709, 1948.

Immunization of Human Beings with Group A Hemolytic Streptococci*

LOWELL A. RANTZ, M.D., ELIZABETH RANDALL, M.A. and HELEN H. RANTZ
San Francisco, California

THE prevention of hemolytic streptococcal respiratory disease is among the most pressing problems confronting the student of infectious disease. Much disability results from acute suppurative illnesses caused by these organisms and the non-suppurative complications that so frequently follow.^{1,2} Ordinary public health methods have failed to control the spread of respiratory infection. The recent development of technics for the sterilization of air and the control of extrahuman reservoirs of infection³ have been of interest but have not been proved to be of value in the suppression of streptococcal disease and are not yet applicable to the population at large.

Sulfonamide chemoprophylaxis of hemolytic streptococcal infection was tested extensively in groups of rheumatic children and in the armed forces,^{4,5} and was successful until epidemics were established in which the causative agents were sulfonamide resistant strains of streptococci.⁶ Under no circumstances could this form of prophylaxis have been widely applied in population groups not under the immediate supervision of physicians because of the hazard of serious toxicity.

Because none of these measures directed toward the prevention of infection of human beings by hemolytic streptococci has been successful, it becomes essential that the usefulness of other measures be explored. The production of active antibacterial immunity by the parenteral administration of a streptococcal vaccine is one of these.

Gabritschewsky, who recognized the streptococcal causation of scarlet fever two decades before other investigators, prepared a vaccine from streptococci isolated from human beings suffering from this disease. This material was administered by him and other European workers to thousands of children in clinical experiments and appears to have been efficacious in reducing the frequency of occurrence of scarlet fever in the immunized groups.⁷ The method of preparation of the material, reactions which followed its use and results of serial Dick testing indicate that the vaccine contained not only streptococci but also large amounts of the erythrogenic substance of Dick. It is almost certain that the administration of this material reduced the incidence of scarlet fever by inducing the formation of antierythrogenic antibody similar to that produced by the injection of Dick toxin. Antibacterial immunity capable of reducing the frequency of hemolytic streptococcus respiratory disease without rash was probably not established.

Since 1924⁸ nearly all investigations of the problem of immunization in streptococcal disease have been directed toward the production of resistance to Dick toxin although it is now well known that these technics do not reduce the total incidence of streptococcal infection.⁹

Bloomfield and Felty¹⁰ used a polyvalent hemolytic streptococcus vaccine for the immunization of a group of nurses and obtained results suggesting that resistance to

* From the Department of Medicine, Stanford University School of Medicine, San Francisco, California. This study was conducted under the auspices of the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Office of the Surgeon General, U. S. Army.

infection by these organisms had been increased. Reactions to the injections were mild.

The intravenous injection of hemolytic streptococci was undertaken some years later by other investigators for the purpose of decreasing the supposed hypersensitivity of rheumatic subjects to the organism, thus alleviating the acute illness and preventing recrudescence.^{11,12,13} In one study the results suggest that recurrences were less frequent and severe in the immunized subjects.¹¹ Whether this was the result of diminished sensitivity or increased resistance to infection of the respiratory passages by hemolytic streptococci cannot be ascertained. The report states that the frequency of respiratory disease in the treated and control groups was similar but the nature of the infectious processes which occurred has not been described. Reactions to administration of the vaccine intravenously were severe in the presence of active rheumatic fever and mild or absent in inactive cases.

Investigation of the structure of the hemolytic streptococci¹⁴ has demonstrated that the organisms pathogenic for man are members of a single serologic group (A) and that the members of this group may be further subdivided into types on the basis of two protein constituents of the bacterial cell, the "T" and "M" substances. Evidence has accumulated, obtained by protection tests in rodents, which indicates that resistance to infection by these streptococci is type specific and closely related to the M-anti-M antibody system.^{15,16} Confirmation of this point of view has been obtained by study of human disease and experimental streptococcal infection in monkeys.¹⁷

Evans in a series of papers^{18,19,20} has objected to the concept of type specific immunity and has presented experimental evidence which suggests strongly that certain strains of group A streptococci have a broad immunologic base and are able to stimulate antibodies capable of conferring protection in mice against streptococci of certain other types. Dubos²¹ has also pointed

out the paucity of information which is available in regard to group rather than type specific resistance to infection by streptococci and pneumococci.

This information indicates the importance of further investigation into the protective value of group specific immunity in streptococcal disease. Type specific resistance to infection is more potent and more easily evaluated epidemiologically and in the laboratory. It is, therefore, appropriate to begin an exploration of the usefulness of antistreptococcal immunization in human beings by studying in man the production of type specific antibodies and resistance to infection.

Two naval epidemiologic units have recently reported experiences in the use of group A hemolytic streptococcus vaccines for the control of respiratory disease in training stations in which epidemics caused by sulfonamide resistant streptococci of a very few types were in progress.²² Heat and ultraviolet-killed organisms were injected three times within a week. Reactions were mild with type 19 vaccine but severe and common when type 17 cells were added. No protection against natural infection by streptococci of the homologous types as the result of immunization was demonstrated in several experiments.

Another approach was adopted in this clinic since it seemed desirable to measure the production of type and group specific antibodies and to study the nature and severity of reactions that would be associated with the immunization of human beings with group A hemolytic streptococci before beginning work in the field.

MATERIALS AND METHODS

Preparation of Vaccine. The organisms used were group A hemolytic streptococci of types 3 and 17 isolated from the throats of infected human beings. They were in the matt phase when used and formed large amounts of acid soluble type specific material.¹⁴ Four liters of a broth culture of each, incubated for eighteen hours, were centrifuged and the sedimentary cells washed once with a large volume of sterile normal salt solution. The cells were again re-

covered by centrifugation, resuspended in 50 ml. of normal salt solution, killed by heat at 60 to 65°C. for sixty minutes in a water bath and preserved with .01 per cent formalin. The material was shaken for three hours in a Kahn shaker to reduce the granularity.

The suspension of type 3 contained 2.2 mg. of bacterial N per ml., that of type 17 contained 4.4 mg. per ml. Bacterial counts were not made of either preparation. Other experience indicates that 1 mg. of streptococcal N is equivalent to approximately 1 billion chains as determined by plate count.

Appropriate serial dilutions were made in sterile normal saline in such a way that the amount of vaccine to be administered was contained in from .1 to .5 ml. All injections were given subcutaneously in the deltoid region.

Antibody Determinations. *Anti-M antibody:* The technic of Rothbard²³ for the detection of anti-M type specific antibody was followed exactly. The single modification was the use throughout of the blood of one adult which permitted excellent growth of the test strains.

Anti-X antibody: An investigation has been conducted and reported in detail elsewhere²⁴ of a non-type specific, precipitating antigen which is present in acid extracts of matt group A streptococcal cells. It is not the "C" carbohydrate. Full details of the method of its preparation, the microprecipitin technic used for detection of its antibody, the antibody response which occurred following hemolytic streptococcal infection and the relationship of this antigen-antibody system to the clinical manifestations of hemolytic streptococcal disease have been presented.

Anti-C antibody: Purified group carbohydrate "C" was used as an antigen for the detection of anti-C precipitating antibody by means of a microtechnic described elsewhere.²⁴

Antistreptolysin: Antistreptolysin titers of the collected sera were measured by a method previously described.²⁵

Study Groups. *Group 1:* Group 1 was composed of ten males and one female, all of whom suffered from serious, disabling disease of the joints or nervous system. All but two were bed- or chair-fast.

Group 2: Group 2 was composed of thirty-two healthy male convicts whose mean age was 30.5 years with a range from eighteen to fifty-six years.

Antibody Response. *Group 1:* Six members of

Group 1 received type 3 and five received type 17 vaccine. An initial test dose of approximately 3 micrograms of N* was administered followed by eight subsequent injections at weekly intervals. Each case was titrated individually, the amount of vaccine being increased irregularly

TABLE I
TYPE SPECIFIC ANTIBODY RESPONSE IN GROUP 1

Total Vaccine Micrograms of N	Type 3		Type 17		Total Cases	
	No. of Sub- jects	No. with Anti- body Re- sponse	No. of Sub- jects	No. with Anti- body Re- sponse	No. of Sub- jects	No. with Anti- body Re- sponse
80 to 90	3	1	1	0	4	1
160 to 190	1	0	2	0	3	0
370 to 520	1	1	1	1	2	2
2,600 to 3,700	1	1	1	1	2	2

TABLE II
X ANTIBODY RESPONSE IN GROUP 1

Total Vaccine Micrograms of N	Type 3		Type 17		Total Cases	
	No. of Sub- jects	No. with Anti- body Re- sponse	No. of Sub- jects	No. with Anti- body Re- sponse	No. of Sub- jects	No. with Anti- body Re- sponse
80 to 90	1	0	0	0	1	0
160 to 190	1	0	1	0	2	0
370 to 520	1	1	1	1	2	2
2,600 to 3,700	1	1	1	1	2	2

Antibody present in 4 initially.

each week on the basis of the severity of reaction to the previous dose. Sera were collected aseptically from each subject before the immunizations were begun and again ten weeks later or one week after the last injection of vaccine.

Seven subjects accepted less than 190 micrograms of N and type specific antibody developed in only one. It was possible to administer from 370 to 3,700 micrograms of N to four subjects, in all of whom a type specific antibody response occurred. (Table I.)

Anti-X antibody developed during immunization in four of the seven subjects in whom it was not present in the initial serum. All of the responses were observed in persons who had received more than 370 micrograms of N. (Table II.) Anti-C antibodies failed to appear as the

* Here and subsequently this indicates that vaccine equivalent to this amount of N was injected.

result of immunization and no significant alteration of the antistreptolysin titer occurred.

Vaccine of both types 3 and 17 was equally capable of stimulating the production of these two antibodies and the quantitative relationships with each were similar.

TABLE III
DOSAGE SCHEDULE IN GROUP 2

No. of Injections of Vaccine at Intervals of 7 Days*	Total Dose of Vaccine in Micrograms of N	Number of Subjects
3	6 to 16	11
3	88 to 124	5
4	8 to 16	3
4	92 to 164	3
5	12 to 20	6
5	144 to 204	4

* Test and subsequent larger dose forty-eight hours later considered as single injection.

Group 2: All of the members of Group 2 received a test dose of 4 micrograms of N. Another injection of 40 micrograms of N was given forty-eight hours later to those who had not reacted strongly to the initial dose. Subsequent injections of vaccine were at seven-day intervals. The amount administered and the duration of the immunization were dictated by the severity of reactions. The number of men who received various courses and quantities of vaccine are summarized in Table III. Sera were collected before the immunization was begun and 8 weeks later. Neither a type specific, anti-X nor anti-C antibody response occurred nor did the antistreptolysin titer vary significantly in any subject.

Toxic Reaction to Immunization. Group 1: It quickly became apparent during the early phase of the immunization of Group 1 that there were very great individual differences in the tolerance of human beings for subcutaneously injected killed streptococci. These persons were so situated that they could not be kept under close observation and the degree of severity of reaction was necessarily determined by questions asked at the time of the subsequent injection. The data obtained are, therefore, not precise, but it is notable that by the fifth week two individuals were comfortably receiving doses of 400 micrograms of N, whereas four were accepting only 8 micrograms of N or less. The same situation prevailed at the end of the

immunization period except that the differences were greater. Two subjects then reacted strongly to the injection of more than 6 micrograms of N and two received 600 to 800 micrograms of N without difficulty.

The toxic phenomena were of three sorts: (1) systemic reactions with chills, malaise and aching; (2) swelling and soreness of the injected arm and (3) nodule formation. The latter complication was of interest. Certain subjects developed firm nodules at the site of injection that persisted for several weeks. They were tender initially but later became painless. Liquefaction of the nodule occurred on two occasions in one individual. The aspirated material from each was sterile. There was no difference in severity of reactions caused by vaccine prepared from the two types of streptococci.

Further description of the reactions to immunization in Group 1 is not feasible because clinical observations were inadequate.

Group 2: The subjects in Group 2 received an initial test dose of type 17 vaccine equivalent to 4 micrograms of N. Local reactions, characterized by erythema, soreness of the arm and occasionally persistent nodule formation in varying combinations occurred in twenty and were graded as severe in six. One of the latter suffered a generalized systemic disturbance as well. Twelve subjects who accepted the test dose without reaction received a ten-fold increment of vaccine (40 micrograms of N) two days after the first injection. Reactions to this amount were minimal or absent in all.

The quantity of vaccine administered each following week was based on the reaction to the test and subsequent injections of the material. None of the six subjects in whom severe reactions occurred initially was able to tolerate more than 2 micrograms of N, and one was ill and required rest in bed after an injection of only 1 microgram of N. Twelve of the fourteen subjects who suffered only a moderate initial reaction were able to accept 2 to 4 micrograms of vaccine as N throughout the planned course. Increasing sensitivity appeared in two. Five of the twelve subjects who did not react to the administration of 40 micrograms of N were able to continue at this level for four to five weeks. The remaining seven developed increased sensitivity to the injection of streptococci.

The development of accentuated reactivity in certain subjects to quantities of vaccine previously accepted without difficulty was notable.

The details of this phenomenon as observed in nine persons are presented diagrammatically in Figure 1.

The administration of 4 micrograms of N to subjects 4 and 18 was not associated initially with marked toxicity. One week later a similar quantity of vaccine invoked a moderately severe

local and general systemic reaction in one and a mild local disturbance in the other. On the following week the dose of vaccine was halved but moderately severe local and generalized reaction occurred in Subject 4 and similar but much more violent response in Subject 18.

A more dramatic sequence of events occurred

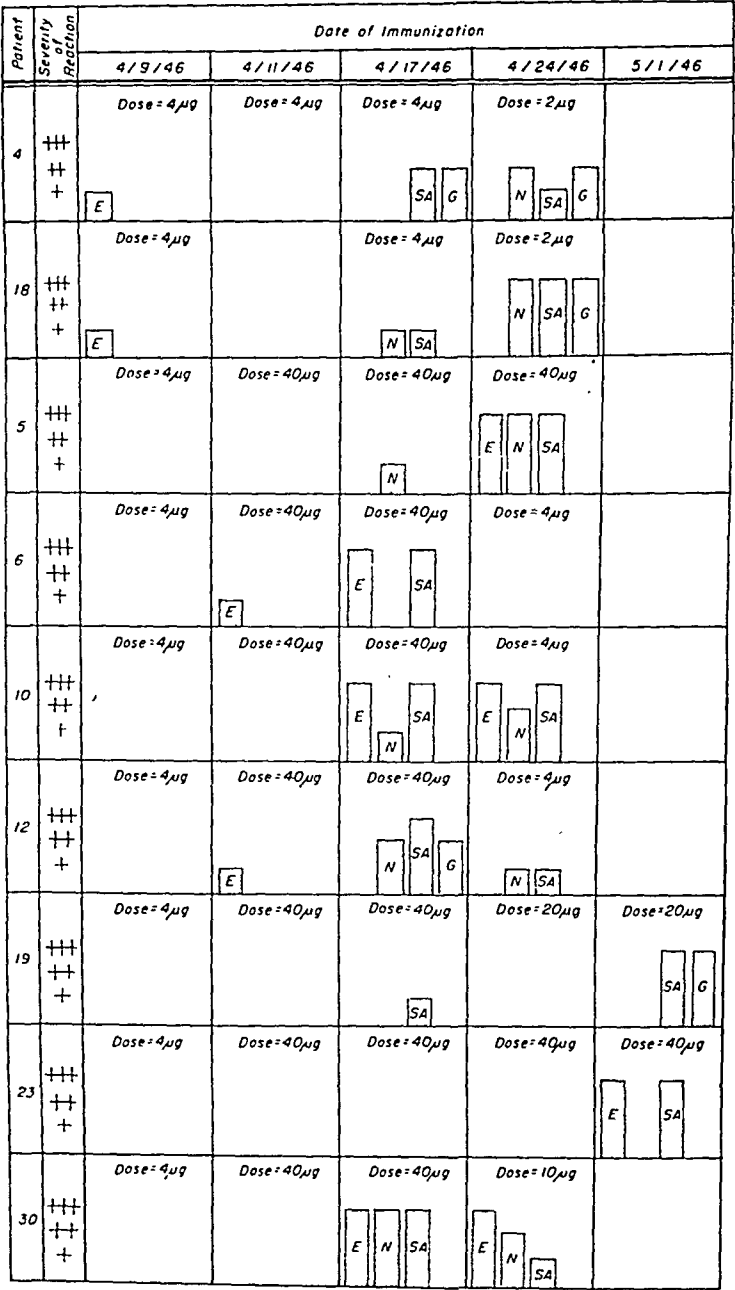


FIG. 1. Increasing reactivity to injection of group A hemolytic streptococci in nine subjects. The dose of injected vaccine is expressed as its equivalent in micrograms of N. Reactions: E, erythema; N, persistent nodule; SA, soreness of arm; G, generalized systemic disturbance. The height of the cross hatched column indicates the severity of the reaction.

in seven subjects who accepted an initial injection (forty-eight hours after the test dose) of 40 micrograms of N without difficulty. Severe local and in two marked generalized systemic reactions followed the second injection of 40 micrograms of N in four, the third in one and the fourth in two subjects. The toxic phenomena in these men consisted of extensive erythema of the skin around and the development of large persistent nodules at the site of injection in association with great local soreness and tenderness of the arm. Generalized systemic reactions with chills and malaise were also observed.

The course of immunization in Subject 10 was particularly interesting since the original injection of 40 micrograms of N caused no toxicity whatever. Two weeks later after his sensitivity to the streptococcus had increased a violent reaction followed the administration of only 4 micrograms of N.

The degree of the initial and the development of subsequent reactivity to the injection of streptococcal vaccine were correlated with the antistreptolysin titer and anti-X precipitin content of the pre-immunization sera obtained from each subject. The mean antistreptolysin titer of the sera of twenty men who responded to the test dose with a severe or moderately severe reaction was 84 units, that in the twelve non-reactors was 43 units.

Five of eleven subjects, or 45.5 per cent, whose initial serum contained anti-X antibody developed an increasing sensitivity to injection of streptococci; only four of twenty-one, or 19.0 per cent, in whom this antibody was absent did so. This is a significant difference but the observation is probably not entirely valid since a smaller number of subjects in whom this antibody was absent tolerated the large amount of vaccine which was most frequently followed by an enhanced reactivity.

COMMENT

An exploratory study of the immunization of human beings with group A hemolytic streptococci has been described. This work was undertaken primarily for the purpose of determining the total quantity of vaccine and duration of immunization that would be required for the production of type specific antibacterial antibodies. These immune substances, as detected by the Rothbard technic, and the non-type

specific anti-X antibody appeared in the serum of only those experimental subjects who accepted 370 micrograms of N or more in nine injections at weekly intervals. Shorter courses and smaller amounts of vaccine failed to induce an antibody response.

The data presented herein suggest that antistreptococcal prophylactic immunization will not be practical or useful if a demonstrable type specific antibody response is essential for its success. Few persons will tolerate the large amount of vaccine that must be administered over a long period of time in order to stimulate the production of these immune substances.

It is quite probable that resistance to infection by hemolytic streptococci can be enhanced by immunization although the procedure does not induce a measurable type specific antibody response. Success or failure of antistreptococcal technics under these circumstances can be studied only when epidemic conditions permit the evaluation of prophylactic methods in the field. This situation, which may well be that existing in man, is cumbersome and greatly limits the possible lines of attack on the problem of prevention of hemolytic streptococcal disease. If an antibody response had occurred regularly, it could have been used as a guide during the study of various prophylactic technics, as has been the case in the investigation of immunization against infection by *S. typhii* and the viruses of influenza A and B.

Toxicity as the result of injection of small numbers of heat killed group A hemolytic streptococci was severe. The reactions which occurred were principally local and consisted of erythema around and persistent nodule formation at the site of injection. It is impossible to determine whether the erythema was the result of reactivity on the part of the subjects to the Dick erythrogenic material which may not have been entirely removed from the streptococcal cells at the time of preparation of the vaccine since none of the experimental subjects was Dick tested.

The formation of persistent large nodules, initially tender but later becoming painless, at the site of injection of the vaccine was of great interest. Their nature cannot be ascertained in the absence of histologic examination. In certain instances generalized systemic disturbances with chills, malaise and aching of the joints were also observed.

The subjects of Group 2, following injection of a small number (circa 4 million cells) of killed group A streptococci, were divisible into two sharply defined groups: those who reacted vigorously to the test dose and those who accepted this and a ten-fold greater amount of vaccine without reaction. The basis for this sharp difference in reactivity cannot be elucidated. It seems wiser to regard the observed toxicity as a reaction to the erythrogenic substance especially since erythema was the principal manifestation of the disorders, until additional experiments have been conducted using a vaccine prepared from repeatedly washed streptococci and tested in subjects whose Dick skin reaction has been determined. The definite possibility exists that the manifestations of toxicity in these men were the result of sensitivity to some other fraction or product of the hemolytic streptococcus.

This position is strengthened by the fact that the mean antistreptolysin titer was higher in individuals who reacted strongly to the test dose than in those who did not, indicating that the former group had been more recently infected by hemolytic streptococci than the latter. This circumstance may have led to a state of more active streptococcal hypersensitivity in these men.

The increasing reactivity to the injection of hemolytic streptococci which was exhibited by certain subjects was of even greater interest than the initial toxicity of these organisms for others. This phenomenon occurred most frequently in those individuals who initially tolerated the administration of a large amount of vaccine without difficulty. Individuals who had received vaccine equivalent to 20 to 40

micrograms of N on one, two, or three occasions without reactions subsequently developed violent disturbances in response to similar or smaller amounts of the immunizing agent. Erythema and generalized systemic reactions were prominent features of these disorders but the formation of persistent nodules was more frequent in these subjects than in those in whom a high initial toxicity to streptococci was observed.

Only one interpretation of these results seems appropriate. The sequence of events in these individuals must be regarded as the result of the development of artificially induced hypersensitivity, presumably of an immunologic nature, to group A streptococci. It is not possible to suggest which antigenic fraction or product of the organism was responsible for the production of the altered tissue reaction.

An earlier analysis indicated that the presence of anti-X antibody in the pre-immunization serum was associated with a higher incidence of developing sensitivity. A more critical examination of the data reveals that subjects in whose sera this substance was initially present more frequently accepted the larger amounts of vaccine that were usually required for the stimulation of an increased reactivity.

The results of this study in human beings are consistent with those obtained in other animals^{26,27} which demonstrated that hemolytic and non-hemolytic streptococci are remarkably effective sensitizing agents when injected locally. Elsewhere²⁸ it was predicted that hypersensitivity might develop if antistreptococcal immunization were undertaken in man and that this might lead to a greater susceptibility to rheumatic fever and other non-suppurative complications of hemolytic streptococcal disease if prophylaxis against infection by hemolytic streptococci was incomplete. This remains a grave possibility.

Theoretic considerations have suggested that the production of active immunity to infection by group A hemolytic streptococci should be most difficult since resistance to infection may be type specific. If this is the

case, a polyvalent vaccine containing cells of all the types of streptococci causing disease in the community would be essential. The information obtained in this study suggests that large numbers of organisms of each type would probably be required in the immunizing preparation and that adequate amounts of the mixture could be administered to few human beings because of its probably high initial toxicity. Added to these difficulties would be the great hazard of sensitization of the immunized persons.

Future investigation of prophylactic immunization against hemolytic streptococcal infection should include experimental study of non-type specific immunity. In addition, chemical methods should be utilized for the purpose of separating the immunizing from the sensitizing and toxic fractions or products of the streptococcus. The route of administration of the immunizing substance should also be evaluated since intravenous injection of the antigen may be less likely to induce sensitization.²⁹ Work along these lines might lead to the development of technics suitable for the control of monotype epidemics in large semi-closed groups, such as those present in schools and the armed forces, even if not applicable to the population at large.

SUMMARY

1. Heat-killed group A hemolytic streptococci were administered subcutaneously to human beings.

2. Type specific and other antibacterial antibodies developed only in those subjects who received a very large amount of vaccine over a nine-week period.

3. Toxic reactions were severe following the injection of small amounts of vaccine in certain persons. Others accepted much larger amounts without difficulty.

4. Increased reactivity to the injection of hemolytic streptococci developed in some subjects. This is believed to represent artificially induced sensitivity of an immunologic type to the streptococcus or its products.

The authors are grateful to Warden Clinton Duffy, Dr. Leo Stanley and those prisoners of San Quentin prison whose voluntary cooperation made this work possible.

REFERENCES

1. RANTZ, L. A., BOISVERT, P. J. and SPINK, W. W. The etiology and pathogenesis of rheumatic fever. *Arch. Int. Med.* 76: 131, 1945.
2. RANTZ, L. A. The natural history of hemolytic streptococcus sore throat. *California Med.*, 65: 266, 1946.
3. ROBERTSON, O. H., HAMBURGER, M., JR., LOOSLI, C. G., PUCK, T. T., LEMON, H. M. and WISE, H. A study of the nature and control of air-borne infection in army camps. *J. A. M. A.*, 126: 993, 1944.
4. Proceedings of Conference on Rheumatic Fever, Washington, D. C., October 5-7, 1943. U. S. Department of Labor, Children's Bureau Publication No. 308. Pp. 64-87. Washington, 1945. U. S. Government Printing Office.
5. The prevention of respiratory tract bacterial infections by sulfadiazine prophylaxis in the United States Navy. NAVMED 284. Bureau of Medicine and Surgery, Navy Department, Washington, D. C., 1944.
6. Epidemiology Unit No. 22. Sulfadiazine resistant strains of beta hemolytic streptococci appearance during the course of sulfadiazine prophylaxis at a large naval training center. *J. A. M. A.*, 129: 921-927, 1945. DAMROSCH, D. S. Chemoprophylaxis and sulfonamide resistant streptococci. *J. A. M. A.* 130: 124, 1946.
7. Vaccine Prophylaxis and Therapy of Scarlet Fever. (In *Annals of the Pickett-Thomson Research Laboratory.*) P. 244, chap. 35, vol. 6. Monograph XI. Baltimore, 1930. Williams and Wilkins Company.
8. DICK, G. F. and DICK, G. Scarlet fever toxin in preventive immunization. *J. A. M. A.*, 82: 544, 1924.
9. JACKSON, R. T. Active immunization against *Streptococcus scarlatinae*. *Irish J. M. S.*, pp. 260-266, July, 1941.
10. BLOOMFIELD, A. L. and FELTY, A. R. Prophylactic vaccination against acute tonsillitis. *Bull. Johns Hopkins Hosp.*, 34: 251, 1923.
11. WILSON, M. G. and SWIFT, H. F. Intravenous vaccination with hemolytic streptococci: its influence on the incidence of recurrence of rheumatic fever in children. *Am. J. Dis. Child.*, 42: 42, 1931.
12. SWIFT, H. F., HITCHCOCK, C. H., DERICK, C. L. and McEWEN, C. Intravenous vaccination with streptococci in rheumatic fever. *Am. J. M. Sc.* 181: 1, 1931.
13. COLLIS, W. R. F. and SHELDON, W. Intravenous vaccines of hemolytic streptococci in acute rheumatism in childhood. *Lancet*, 2: 1261, 1932.
14. LANCEFIELD, R. C. Specific relationship of cell composition to biological activity of hemolytic streptococci. In *Harvey Lectures 1940-41*. Baltimore, 1941. Williams & Wilkins Company.
15. HIRST, G. K. and LANCEFIELD, R. C. Antigenic

- properties of the type specific substance derived from group A hemolytic streptococci. *J. Exper. Med.*, 69: 425, 1939.
16. LANCEFIELD, R. C. Type specific antigens M and T of matt and glossy variants of group A hemolytic streptococci. *J. Exper. Med.*, 71: 521, 1940.
 17. WATSON, R. F., ROTHBARD, S. and SWIFT, H. F. Type-specific protection and immunity following intranasal inoculation of monkeys with group A hemolytic streptococci. *J. Exper. Med.*, 84: 127, 1946.
 18. EVANS, A. C. Cross protection between heterologous agglutinogenic types of beta hemolytic streptococci. *J. Immunol.*, 42: 15, 1941.
 19. EVANS, A. C. Cross protection between heterologous agglutinogenic types of beta hemolytic streptococci of group A; immunogenic group of 4 types. *J. Immunol.*, 46: 399, 1943.
 20. EVANS, A. C. Protection between strains of heterologous agglutinogenic types of beta hemolytic streptococci of group A. III. Further observations. *J. Immunol.*, 52: 1, 1946.
 21. DUBOS, R. J. *The Bacterial Cell*. Chap. VII, p. 240; chap. IX, p. 346. Cambridge, 1945. Harvard University Press.
 22. YOUNG, D. C., BREESE, B. B. et al. Failure of type specific streptococcus pyogenes vaccine to prevent respiratory infections. *U. S. Nav. M. Bull.*, 46: 709, 1946.
 23. ROTHBARD, S. Bacteriostatic effect of human sera on group A streptococci. I. Type-specific antibodies in sera of patients convalescing from group A streptococcal pharyngitis. *J. Exper. Med.*, 82: 93, 1945.
 24. RANTZ, L. A. Antibacterial precipitating antibodies in group A hemolytic streptococcus sore throat. *Am. J. Med.*, (in press).
 25. RANTZ, L. A. and RANDALL, E. A modification of the technique for the determination of the anti-streptolysin titer. *Proc. Soc. Exper. Biol. & Med.*, 59: 22, 1945.
 26. ANDREWS, C. H., DERICK, C. L. and SWIFT, H. F. The skin response of rabbits to non-hemolytic streptococci. I. Description of a secondary reaction occurring locally after intradermal inoculation. *J. Exper. Med.*, 44: 35, 1926.
 27. ANGEVINE, D. M. Differences in immunization and sensitization in rabbits injected with relatively avirulent or highly virulent cultures of same strain (H) of hemolytic streptococcus. *J. Exper. Med.*, 69: 211, 1939.
 28. RANTZ, L. A. Public health and preventive aspects of streptococcal infections. *California & West. Med.*, 63: 5, 1945.
 29. SWIFT, H. F. and DERICK, C. L. Reactions of rabbits to nonhemolytic streptococci. II. Skin reactions in intravenously immunized animals. *J. Exper. Med.*, 49: 883, 1929.

Treatment of Acute Rheumatic Fever with Aspirin*

With Special Reference to the Biochemical Changes

WILLIAM S. HÖFFMAN, M.D., MARK POMERANC, M.D., ITALO F. VOLINI, M.D.

and CATHERINE NOBE, B.S.

Chicago, Illinois

SALICYLATES have remained the drug of choice in the treatment of acute rheumatic fever ever since MacLagen¹ introduced the use of salicin in this disease. It is a commonly recognized fact that adequate doses of salicylates produce a prompt remission of fever and swelling in the joints and prevent extension of the disease process. It is believed by Coburn² and others that prompt suppression of the rheumatic inflammation may prevent development of cardiac manifestations of the disease. Murphy³ however, could find no anatomic evidence of the ameliorating effect of salicylates.

The most common method of administering salicylates has been in the form of sodium salicylate. Large doses have been prescribed for over forty years. Lees⁴ in 1903 recommended doses of 150 to 200 gr. (10 to 13.3 Gm.) daily. Coburn,⁵ utilizing an accurate method for the determination of plasma salicylate, laid down criteria for adequate treatment. He believed that the dose should be high and frequent enough to produce and maintain a plasma salicylate level of 36 mg. per 100 cc. (360 micrograms per cc.) and thought that this could be best accomplished by intravenous injection. The gastric irritation frequently accompanying peroral administration of sodium salicylate has led to the prescription of sodium bicarbonate along with sodium salicylate. This modification became all the more popular because symptoms of salicylism

were less likely to occur with its use. It is now recognized, however, that salicylism is avoided when bicarbonate is used because the plasma salicylate levels are lowered.

Because of the gastric irritation frequently encountered with sodium salicylate medication, many clinicians have tended to use aspirin in high doses in the treatment of acute rheumatic fever. However, there are few published reports of its use.⁶ Recently, during the course of the clinical evaluation of a new aspirin tablet containing aluminum hydroxide, an opportunity presented itself for study of the effect of aspirin in high doses on the course of acute rheumatic fever and of some of the biochemical changes that occur during its administration. This report deals particularly with the findings in respect to sedimentation rate, prothrombin concentration and acid-base balance.

METHODS

One hundred successive adult patients with acute rheumatic fever were treated with doses of aspirin estimated to produce and maintain plasma salicylate concentrations of 30 to 35 mg. per 100 cc. (300 to 350 micrograms per cc.). All these patients had the usual criteria of the disease: sudden onset of pain, swelling and tenderness in multiple joints with fever and rapid sedimentation rate. Some were seen in the first attack; many others had had previous episodes; a number had evidence of rheumatic carditis. In only eighty of these were extended chemical studies made, and these form the basis for this report.

* From the Hektoen Institute for Medical Research of the Cook County Hospital. This work was supported by a grant from The Wander Co., Chicago, Ill. and A. Wander, Ltd., London, England.

At weekly intervals venous blood samples were drawn under oil and the serum analyzed for the following constituents: sodium by the method of Hoffman and Osgood,⁷ chloride by the method of Schales and Schales,⁸ bicarbonate by the volumetric method of Van Slyke⁹ with

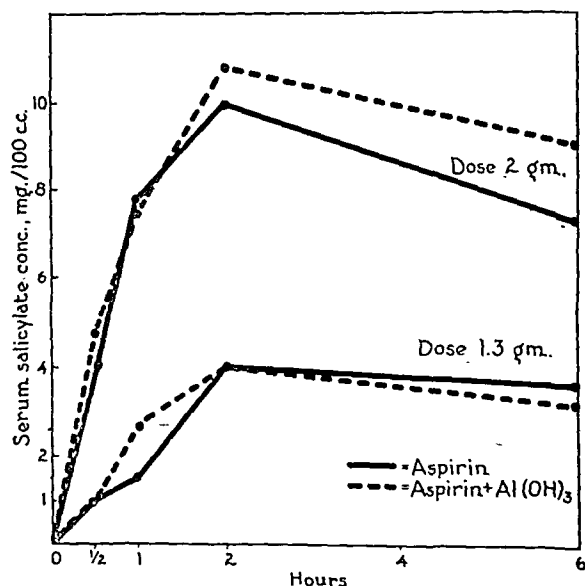


FIG. 1. Plasma salicylate concentrations after single doses of aspirin with and without aluminum hydroxide.

the assumption of a pH of 7.4, sedimentation rate corrected for anemia according to Wintrobe¹⁰ and prothrombin concentration by the Quick¹¹ method calculated as percentage of normal based on a normal control. Serum salicylate determinations were made by the method of Brodie, Udenfriend and Coburn⁵ by ethylene dichloride extraction. Urinary partitions of salicylate were estimated by the scheme of Smith and his co-workers.¹² In a number of patients blood pH determinations were made at the bedside with the aid of a Coleman pH meter calibrated at 38°C.

The aspirin used for this study was Alasil,* tablets containing 4 gr. of aspirin, 2 gr. of colloidal aluminum hydroxide and an excipient. Control tablets of aspirin were also used which were of the same size and which contained 4 gr. of aspirin but 2 gr. of starch instead of aluminum hydroxide. Preliminary tolerance curve experiments as illustrated in Figure 1 demonstrated that the plasma salicylate levels achieved after single doses of either form of aspirin were essentially the same. Of sixty-five patients given the control tablets in the high therapeutic doses eight (or 13 per cent) complained of local

gastric distress or heartburn. These symptoms were relieved when the tablets containing aluminum hydroxide were substituted for the control tablets without the knowledge of the patient. However, as will be seen later, many of these patients developed salicylism with either form of aspirin if the plasma salicylate level was high enough. It was not easy at this stage to distinguish between the distress due to local irritation and the nausea and vomiting of cerebral or systemic intoxication. Since the plasma salicylate levels and other chemical findings were indistinguishable when aspirin with or without aluminum hydroxide was used, the remainder of the paper will be made without reference to the presence or absence of aluminum hydroxide in the medicament although for most of the period of study of each patient he was receiving the aluminum hydroxide-aspirin combination.

RESULTS

Clinical Response to Aspirin. On dosages ranging from 4 to 6 tablets every four hours (96 to 144 gr. per day depending on the weight, or about 128 mg. per day per Kg. of body weight) the patients usually experienced relief of fever, pain and tenderness in the involved joints in twenty-four to forty-eight hours, even before the plasma salicylate concentration had risen to levels of 30 or more mg. per 100 cc. Such concentrations were usually achieved by the third day by this method of medication. Thus, the analgesic and antipyretic effect of the salicylate could be accomplished without high plasma salicylate concentrations. To produce these effects it was not necessary to employ intravenous injections or the hourly oral doses so popular in the past. Once the desired plasma level had been achieved it could be maintained by the same dose of 4 to 6 tablets given every six hours instead of every four hours. Complete subsidence of the swelling and mobility of the joints usually followed soon after the relief of pain. The patients were kept in the hospital until they were clinically well, but many had to be discharged before the sedimentation rate had returned to normal. The hospital stay ranged from fourteen to

* Supplied by the House of Wander.

eighty-seven days with an average of thirty-six days. Those who stayed for thirty or more days usually had findings of acute cardiac involvement, some with increased P-R intervals in the electrocardiogram and others with pericarditis. The response of these patients to salicylate therapy was slow but their symptoms finally subsided without any other medication.

Salicylism. Almost all patients in whom levels of 30 to 40 mg. per 100 cc. were maintained for several days developed one or more of the symptoms of salicylism. These included tinnitus, partial deafness, pounding in the head, nausea and vomiting and a general feeling of intoxication. As in alcoholic intoxication, mental disturbances were often manifested by excitability, negativism and irresponsibility, as recently described by Huntington et al.¹³ It was at this stage that many patients refused to cooperate in taking the medication. They used various subterfuges to avoid swallowing the tablets which they recognized as having a causal relation to their new symptoms. In this respect aspirin was no different from sodium salicylate. With either medication, if sufficiently high plasma salicylate concentrations were reached, symptoms of salicylism were likely to occur. Moreover, when sodium bicarbonate was given in addition to the aspirin, relief of symptoms occurred only because of the lowering of the salicylate levels. If higher doses of aspirin were then given and the plasma levels allowed to attain their previous high values, salicylism recurred in spite of bicarbonate medication.

In the uncooperative patient failure to take the medication continuously could often be ascertained only by a rapid drop in the plasma salicylate levels. The patient was often able to hide from the nurse the fact that he had not swallowed the tablets. The importance of frequent plasma salicylate determinations as a guide to effective rheumatic fever therapy is thus clearly indicated as is one of the chief advantages of the intravenous therapy recommended by Coburn. When the plasma salicylate level was found to be low, cooperation could

usually be effected, by the use of smaller doses. Thus, the eighty patients in the study could be divided into two groups: forty-one patients in whom the average plasma salicylate level was maintained above 25 mg. per 100 cc. and thirty-nine in whom the

TABLE I

EFFECT OF ASPIRIN THERAPY ON SEDIMENTATION RATE	
Total no. of patients with initially elevated sedimentation rate	80
i. No. of patients with average salicylate levels above 25 mg. per 100 cc.	41
No. of patients with sedimentation rate normal at discharge	23
No. of patients with sedimentation rate still elevated at discharge	18
ii. No. of patients with average salicylate below 25 mg. per 100 cc.	39
No. of patients with sedimentation rate normal at discharge	17
No. of patients with sedimentation rate still elevated at discharge	22

average level was below 25 mg. per 100 cc. This involuntary division was made the basis for a comparative evaluation of high or moderate salicylate doses.

Sedimentation Rate. The sedimentation rate of all the rheumatic fever patients was high at the time of admission. It usually ranged between 30 and 40 mm. per hour after correction for anemia. In a few instances the sedimentation rate fell rapidly but never so fast as the fever and swelling. In many patients the sedimentation rate was still elevated at the time of discharge from the hospital when all clinical symptoms had already disappeared. Comparison of the effect of high and low plasma salicylate concentrations on the sedimentation rate (Table I) showed only a slight superiority of the high levels in reducing the sedimentation rate to normal by the time clinical symptoms had completely disappeared. Seventeen of thirty-nine patients were able to achieve this result with moderate levels, as had been found by Manchester,¹⁴ while twenty-three of forty-one accomplished it on average levels higher than 25 mg. per 100 cc.

Prothrombin Levels. The concentration of prothrombin was expressed for convenience as inversely proportional to the prothrombin time rather than on the basis of a prothrombin curve. The error involved in this

assumption is not important for moderate reductions of prothrombin. Ever since Link¹⁵ showed that salicylate was a probable end product of the metabolism of dicumarol, a fear has been created that salicylate therapy can produce a hemor-

TABLE II
EFFECT OF ASPIRIN THERAPY ON PROTHROMBIN LEVEL

Total No. of Patients.....	66
i. No. of patients with average salicylate level above 25 mg. per 100 cc....	31
No. of patients with prothrombin below 75 per cent.....	10 (32%)
No. of patients with prothrombin above 75 per cent.....	21 (68%)
ii. No. of patients with average salicylate levels below 25 mg. per 100 cc.....	35
No. of patients with prothrombin below 75 per cent.....	12 (34%)
No. of patients with prothrombin above 75 per cent.....	23 (66%)

rhagic tendency by lowering the prothrombin concentration. Several reports^{16,17} have intimated such an effect, especially in children. Weekly prothrombin time estimations were made in sixty-six of our patients. In general it was found that there was very little change in the prothrombin levels whether the patients were on high or on low doses of aspirin. In only 33 per cent of the patients was there a fall below 75 per cent of normal. Even in these instances the drop was usually moderate and the level tended to return to above 75 per cent of normal with continuation of the medication. No relationship could be found between the incidence of lowered prothrombin levels and plasma salicylate concentrations (Table II), the same percentage being found in the high and in the low plasma salicylate groups. In only one instance was there a fall of prothrombin to a dangerously low level. Here the concentration was calculated as 20 per cent of normal. The only clinical manifestation of hemorrhagic tendency which this patient manifested was a prolongation of the menstrual period. This bleeding was promptly stopped by the injection of two ampules of vitamin K (9.6 mg.). Thereafter the patient's prothrombin level remained in the normal range with continued aspirin therapy and

no further administration of vitamin K. At the time of the prolonged menses the plasma salicylate level was only 19.8 mg. per 100 cc. Thus, these data do not support the claim of Link and others that salicylate therapy has a specific effect upon prothrombin concentration. The isolated instances of a tendency toward bleeding can be more reasonably regarded as manifestations of idiosyncrasy.

Acid-base Balance. Serum chloride, sodium and bicarbonate determinations were made weekly during the course of salicylate therapy. Most patients experienced a moderate reduction of serum bicarbonate. If the lowest serum bicarbonate value found for each patient was chosen, twenty-four patients had values below 40 vols. per 100 cc. (18 mEq. per L.), forty-seven had levels between 40 and 50 vols. per 100 cc. (18 to 20 mEq. per L.) and nine had levels above 50 vols. per 100 cc. (Table III). The bicarbonate levels had no determining effect upon the incidence of salicylism, except in so far as low bicarbonate concentration was more likely to occur with high plasma salicylate. Salicylism occurred with both high and low bicarbonate. Its appearance seemed to be related only to the plasma salicylate concentration as previously mentioned.

Serum chloride concentration was found to be elevated in the majority of instances, the highest levels being found in the group with the lowest bicarbonate concentration. The range of chloride values found in each patient at the time of lowest serum bicarbonate was from 98.6 to 118 mEq. per L., the overall average being 108.6. In the group of low bicarbonate levels (below 40 vols. per 100 cc.) serum chloride averaged 110 mEq. per L. Serum sodium concentrations, on the other hand, were usually within normal limits but on the low side. The range was from 134 to 147 mEq. per L., the average being 140.3 for all the patients and only slightly lower (139.8) in the patients with serum bicarbonate below 40 vols. per 100 cc. These findings, which are summarized in Table III, are similar to

those found by Guest, Rapaport and Roscoe.¹⁸

Blood pH determinations were not made until near the end of the study. In fifteen patients in whom the pH determination was made at the bedside at the time of high

were then repeated. Urine pH determinations were made in both experiments. The details of these experiments will be reported elsewhere.

The clearance of salicylate and chloride before and after bicarbonate could not be

TABLE III
ACID-BASE FINDINGS DURING ASPIRIN THERAPY

	No. of Cases	Lowest Serum Bicarbonate mEq./L.		Serum Chloride mEq./L.		Serum Sodium mEq./L.		pH	
		Range	Average	Range	Average	Range	Average	Range	Average
Total	80	14-25	19	98.5-118.5	108.6	134-147	140.3		
	24	14-18	..	101-118.5	110.1	134-145	139.8		
	47	18-22	..	100-114.3	107.0	134-146	140.4		
	9	22-25	..	98.5-110.5	104.1	137-146	141.0		
Blood pH	15	7.30-7.51	7.41
Urine pH	30	4.88-6.60	5.42

plasma salicylate levels the values ranged between 7.30 and 7.51 with an arithmetical mean of 7.41. (Table III.) These values appeared to show little deviation on either the acid or basic side of normal in spite of the lowered serum bicarbonate.

Determinations were made of the pH of freshly passed urine specimens in thirty patients at the height of the aspirin therapy. The urine pH ranged from 4.88 to 6.30. However, there were only two values above 6.00. The arithmetical mean was 5.42.

Salicylate and Chloride Clearance. To determine whether there was any relation between chloride and salicylate excretion and what the effect on alkali was on these, a series of clearance studies were carried out on twelve patients during convalescence from acute rheumatic fever and while still in aspirin therapy. Plasma and urinary salicylate determinations were made by ethylene dichloride extraction in duplicate one-hour clearance tests. Chloride and creatinine clearances were likewise determined. After these tests the subjects were placed on an alkalinizing regimen, 2 to 3.3 Gm. of sodium bicarbonate every six hours for three days, in addition to the regular aspirin doses. The clearance tests

compared directly because the creatinine clearances were found to be lowered by the alkalinizing regimen. To rule out the effect of altered glomerular filtration the salicylate and chloride clearances were expressed as percentages of the simultaneously determined creatinine clearances. When the apparent salicylate clearance was determined on the basis of the ethylene dichloride extraction and expressed as the percentage of the creatinine clearance (called S/C), the values ranged from 1.36 to 5.78 for urines the pH of which ranged from 4.98 to 5.99. In the urine of pH of 6.60 the S/C was 9.51, and in that with pH of 6.68 the S/C was 11.7. After alkalinization the urinary pH ranged from 6.22 to 7.98. The S/C values rose in all cases, the lowest value of 6.62 being found with the urine of pH 6.22 and the highest of 33.3 for a urine of pH 6.98. In general the clearance was increased three to eight times by alkalinization. Chloride clearances, similarly expressed as percentages of the creatinine clearance, Cl/C, ranged from 6.5 to 3.16. On the alkaline regimen, chloride clearance was increased significantly in seven of twelve experiments as might have been expected;¹⁹ but in five experiments there

was either little change or slight depression of the chloride clearance.

During the course of these clearance experiments the work of Smith and his co-workers¹² on the fractionation of the urinary salicylate came to our attention.

salicylate was markedly increased, it became apparent that the principal effect of alkalization was on the excretion of free salicylate rather than on the conjugated derivatives. These findings are in general agreement with those of Smith and his

TABLE IV

SALICYLATE AND CHLORIDE CLEARANCES AND DISTRIBUTION OF URINARY SALICYLATE DURING ASPIRIN THERAPY WITH AND WITHOUT SODIUM BICARBONATE

Case	NaHCO ₃	Urine pH	Serum Chloride mEq./L.	Plasma Salicylate mg./100 cc.	Creatinine Clearance cc./min.	Cl/C*	Apparent† S/C	Apparent‡ SA/C	SA§ mg./100 cc.	SU§ mg./100 cc.	ST§ mg./100 cc.	SA/ST
1	None	5.99	104.7	29.5	94.3	1.73	3.13	1.95	12.8	13.9	60.6	0.21
	13.3 Gm. daily	7.14	93.5	6.0	63.9	5.66	23.5	17.2	13.5	9.8	39.1	0.35
4	None	5.70	100.2	29.0	91.2	0.98	4.28	2.68	15.7	21.1	88.9	0.18
	13.3 Gm. daily	7.55	105.0	16.1	86.4	1.23	26.8	22.9	116.8	19.3	189.2	0.62

* Cl/C = Chloride clearance ÷ creatinine clearance ratio.

† Apparent S/C = ratio of salicylate clearance to creatinine clearance when the salicylate clearance is calculated from plasma and urine salicylate concentration determined by ethylene dichloride extractions and no account is taken of the bound portion in the plasma.

‡ Apparent SA/C = same as S/C except that salicylate clearance is determined from free salicylate in urine (SA).

§ SA = free salicylate concentration in urine; SU = salicylurate concentration in urine; ST = total salicylate concentration in urine.

Smith's technic involved extraction of urine with both ethylene dichloride and carbon tetrachloride and calculation of the urinary salicylate in terms of free salicylate, salicylurate and total salicylate from empirically derived equations. Fractionations were made by this method in six of the twelve clearance experiments. If the salicylate clearances were estimated on the basis of the free salicylate excreted and again expressed as percentages of the creatinine clearances, the values found ranged from 0.84 to 2.43. However, during alkali administration these values rose to values two to eight times as high. Thus, there was no doubt that salicylate excretion for any given plasma salicylate level was markedly increased when more base was available for urinary excretion. Since on the alkaline regimen the ratio of free salicylate to total

co-workers. Representative data in two experiments are shown in Table iv.

COMMENTS

The clinical and laboratory findings in the eighty patients with rheumatic fever in whom intensive studies were made are in accord with the prevailing view that aspirin in large doses is a convenient and satisfactory form of salicylate medication. The local gastric irritation so often found with sodium salicylate occurred only occasionally in these patients and it was avoided completely when the tablets containing aluminum hydroxide were used. There were no recognizable untoward effects, locally or systemically, from the aluminum hydroxide. The ease with which the desired salicylate levels were achieved and maintained confirmed the findings with single doses that

salicylates are promptly absorbed from the intestinal tract. Since it has already been shown by Lester et al.,²⁰ and confirmed in unpublished studies by us, that the salicylate found in the blood after a dose of aspirin is almost entirely free salicylate, there is no contraindication to the use of aspirin on this score. In fact, Lester believes that the small quantities of acetylsalicylic acid found for a short time in the blood after a dose of aspirin have a greater analgesic effect than does free salicylate. Another advantage of the use of aspirin, with or without aluminum hydroxide, is that it is unnecessary to administer sodium bicarbonate. A still further advantage will be recognized later in the discussion.

The absence of serious increases in the prothrombin time in this group of patients is heartening for recent reports of the possible hemorrhagic danger of salicylate therapy have tended to discourage its use. Since at present the only effective remedy in acute rheumatic fever is salicylate in one form or another, it would be unfortunate if physicians were deprived of its use on inadequate grounds. The occasional patient who shows an unusual lowering of prothrombin concentration with a tendency toward bleeding can easily be treated with vitamin K. Whether aspirin (or aspirin with aluminum hydroxide) produces less alteration of the prothrombin time than sodium salicylate could not be determined, but it has been our general impression that in the many hundreds of patients treated with sodium salicylate in this hospital very little hemorrhagic tendency has been encountered.

The original plan of therapy in this study was to give doses of aspirin high enough to maintain the plasma levels recommended by Coburn. This procedure was found impossible by oral therapy in almost one-half of the subjects. In these patients a compromise was reached in which the patients were given doses that would keep the plasma levels just below salicylism. This dose was 12 to 20 gr. (0.8 to 1.3 Gm.) every four hours until the desired level had been reached and then the same dose every six

hours. In these patients maintained at plasma salicylate levels between 20 and 25 mg. per 100 cc. the therapeutic results were only slightly less satisfactory than those with higher doses. From a practical point of view, it may be safer to use moderate doses and have the assured cooperation of the patient than to insist on the high doses which require constant vigilance and frequent plasma salicylate determinations.

The significance of the lowered serum bicarbonate found during salicylate therapy remains controversial. Does salicylate ingestion produce a primary alkalosis due to respiratory stimulation with compensatory fall in bicarbonate or does it produce a primary fixed acid acidosis with compensatory respiratory stimulation? That toxic doses of salicylate, especially in children, produce marked hyperpnea is well recognized. In a recent case of aspirin poisoning in an eighteen month old child seen by us, we encountered a respiratory rate of more than 70 per minute, far greater than is seen in diabetic coma. Such respiratory stimulation with elevated serum pH has been reported by Coombs et al.²¹ and also by Ryder et al.²² who also found an alkaline urine. In experimental salicylate intoxication in dogs, Rapaport and Guest²³ as well as Boyle et al.²⁴ were able to demonstrate an initial rise in the serum pH followed by a fall in serum bicarbonate with a compensated return of the pH toward normal. Guest et al.,¹⁸ in a clinical study of children with rheumatic fever treated with sodium salicylate, presented further evidence that the primary effect was respiratory stimulation with alkalosis. They regarded both the lowering of bicarbonate and the retention of chloride as secondary compensatory phenomena.

On the other hand, Erganian et al.²⁵ found a lowered serum pH and thus acidosis in thirteen cases of salicylate intoxication in infants. Dodd²⁶ had similar findings. Our own data offer no support to the idea of primary alkalosis. The pH of the blood was usually about normal, and there were as many deviations to the acid side as to the

basic. Also, hyperpnea was not a noticeable feature of the symptomatology of our patients during any stage of therapy. Furthermore, alkaline urines were never encountered. For the most part, the urine specimens were highly acid even though ketone bodies were seldom seen in these adult patients. Like Rapaport and Guest we found a tendency toward elevated serum chloride concentrations with normal or slightly lower than normal serum sodium concentrations. Since the plasma salicylate at levels of 40 mg. per 100 cc. produced a displacement of only 3 mEq. of bicarbonate per L. and since no retention of other acids was seen, the lowered bicarbonate was evidently related to the elevated chloride and slightly lowered sodium. These findings associated with acid urine are consistent with those of a fixed acid acidosis.

It is possible to achieve a harmonious explanation of these apparently irreconcilable findings in a manner similar to that offered by Erganian et al.²⁵ A rapid rise in plasma salicylate concentration, especially like that seen in salicylate poisoning in children or in experimental salicylate infusion into animals, has as its primary pharmacodynamic action a stimulation of the respiratory center with rapid removal of free carbonic acid and production of an alkalosis of carbonic acid deficit. Compensation tends to take place by neutralization of base bicarbonate by the plasma proteins and particularly by hemoglobin. The ultimate compensation is by excretion of alkali in the urine. However, independent of this action of salicylate, is its own acidifying action and its effect in increasing the excretion of sodium and retention of chloride. These latter phenomena would produce an acidosis which would require for compensation a respiratory stimulation which has already been produced independently. Thus, the two actions of salicylate are mutually compensatory, and the net effect is a blood pH nearly normal in the presence of lowered bicarbonate and elevated chloride. An additional compensation may be the expansion of extracellular space

including plasma volume as recently reported by York and Fisher.²⁷ If the accumulation of salicylate is relatively slow, as in our patients, the primary hyperventilation may be slight and the acidosis effect more significant. Individual sensitivity of the respiratory center, too, may be a determining factor in production of the primary alkalosis.

Our clearance studies show that salicylate, like chloride, has a very low clearance. Even if, as Smith and Lester have pointed out, only about one-fourth of the plasma salicylate is in the unbound state when the concentration is about 30 mg. per 100 cc. (the remainder being bound to serum proteins), the clearance of salicylate is still very small compared with that of creatinine. Apparently most of the unconjugated salicylate filtered through the glomeruli is reabsorbed by the tubules unless an excess of base is available for simultaneous excretion with it. Under these circumstances it may be that both chloride and salicylate compete for the limited amount of base available for excretion, and when the urine is highly acid both chloride and salicylate are reabsorbed and retained. When extra alkali is furnished and the urine pH rises considerably, much larger quantities of salicylate can be excreted. In the majority of experiments it was possible to demonstrate that chloride under these circumstances was also better excreted. Thus, the acidosis effect of salicylate can be explained by the enforced retention of both salicylate and chloride.

If the acidifying effect of salicylate serves as compensation for the primary hyperpnea, it is apparent that aspirin which is administered as a free acid without sodium is preferable to sodium salicylate in producing this action. This may be why in our patients we could not corroborate the high blood pH values reported by Guest and Rapaport. Conversely, in aspirin or salicylate poisoning administration of sodium bicarbonate is mandatory in spite of any primary alkalosis for the only rapid way to lower the plasma salicylate concentration

is to alkalinize the urine. In the case of salicylate poisoning just mentioned, rapid amelioration of symptoms was produced by administration of glucose and sodium lactate intravenously and of sodium bicarbonate by stomach tube in what appeared to be a dying baby. This treatment is in accordance with that recommended by Barnett et al.²⁸ The fear expressed by Krasnoff and Bernstein²⁹ of using sodium bicarbonate by stomach tube because of the danger of increasing the absorption of whatever salicylate is still in the stomach is unfounded since the amount absorbed is small compared to the increased excretion due to the alkali.

SUMMARY

Eighty adult patients with acute rheumatic fever were treated with aspirin until disappearance of clinical symptoms of the disease. Of sixty-five patients started with control tablets of aspirin eight complained of gastric distress following ingestion. This distress disappeared when tablets containing aspirin and aluminum hydroxide were substituted. For most of the period of therapy in all patients, aspirin plus aluminum hydroxide was administered.

Some symptoms of salicylism occurred in almost all patients when the plasma salicylate level was more than 30 mg. per 100 cc. Only forty-one patients could be maintained at this level; thirty-nine had to be given doses that produced levels under 25 mg. per 100 cc. The sedimentation rate subsided to normal in a slightly larger proportion of patients in the group with high plasma salicylate levels.

The prothrombin concentration was only slightly affected by aspirin therapy. A drop below 75 per cent of normal occurred in one-third of the cases, there being no difference in incidence in the high or moderate dose groups.

A moderate fall in serum bicarbonate occurred in most cases, associated with an elevated serum chloride and a slightly diminished serum sodium. The blood pH was usually normal. The urine was usually

acid. It is believed that salicylate produces a primary hyperpnea with alkalosis but that the accumulated salicylate produces a fixed acid acidosis and that the two effects are mutually compensatory.

The apparent salicylate clearance after aspirin therapy is only about 3 per cent of the creatinine clearance when the urine is highly acid. It increases three to eight times when the urine is alkalinized with sodium bicarbonate. Most of this increase is in free salicylate. Alkalinization is therefore of prime importance in the treatment of salicylate poisoning.

REFERENCES

1. MACLAGEN, T. J. *Rheumatism, Its Nature and Pathology*. New York, 1886. Wm. Wood & Co.
2. COBURN, A. F. Salicylate therapy in rheumatic fever: A rational technique. *Bull. Johns Hopkins Hosp.*, 73: 435, 1943.
3. MURPHY, G. E. Salicylate and rheumatic activity. *Bull. Johns Hopkins Hosp.*, 77: 1, 1945.
4. LEES, D. B. The treatment of some acute visceral inflammations. *Brit. M. J.*, 2: 1318, 1903.
5. BRODIE, B. B., UDENFRIEND, S. and COBURN, A. F. The determination of salicylic acid in plasma. *J. Pharmacol. & Exper. Therap.*, 80: 114, 1944.
6. CECIL, R. L. The therapy of rheumatic fever. *J. A. M. A.*, 114: 1443, 1940.
7. HOFFMAN, W. S. and OSGOOD, B. A photoelectric method for the microdetermination of sodium in serum and urine by the uranyl zinc acetate precipitation. *J. Biol. Chem.*, 124: 347, 1938.
8. SCHALES, O. and SCHALES, S. Simple and accurate method for determination of chloride in biological fluids. *J. Biol. Chem.*, 140: 879, 1941.
9. PETERS, J. P. and VAN SLYKE, D. D. *Quantitative Clinical Chemistry*. Vol. 2, p. 295. Baltimore, 1932. Williams and Wilkins Co.
10. WINTROBE, M. M. and LANDSBERG, J. W. Standardization technique for blood sedimentation test. *Am. J. M. Sc.*, 189: 102, 1935.
11. QUICK, A. J. The prothrombin in hemophilia and in obstructive jaundice. *J. Biol. Chem.*, 73: 109, 1935.
12. SMITH, P. K., GLEASON, H. L., STOLL, C. G. and OGORZALEK, S. Studies on the pharmacology of salicylates. *J. Pharmacol. & Exper. Therap.*, 87: 237, 1946.
13. HUNTINGTON, R. W., JR., RYAN, R. D., BUTT, H. R., GRIFFITH, G. C., MONTGOMERY, H., STOLLEY, F. F. and LEAKE, W. H. Studies in rheumatic fever. II. Absorption of salicylates. *Ann. Int. Med.*, 24: 1029, 1946.
14. MANCHESTER, R. C. Rheumatic fever in naval enlisted personnel. *J. A. M. A.*, 131: 209, 1946.
15. LINK, K. P., OVERMAN, R. S., SULLIVAN, W. R., RUEBNER, C. F. and SCHUL, D. D. Studies on hemorrhagic sweet clover disease. XI. Hypoprothrombinemia in the rat induced by salicylic acid. *J. Biol. Chem.*, 147: 463, 1943.

16. SHAPIRO, S. Studies on prothrombin. vi. The effect of synthetic vitamin K on the prothrombinopenia induced by salicylate in man. *J. A. M. A.*, 125: 546, 1944.
17. FASHENA, G. J. and WALKER, J. N. Salicylate intoxication: studies on the effects of sodium salicylate on prothrombin time and alkali reserve. *Am. J. Dis. Child.*, 68: 369, 1944.
18. GUEST, G. M., RAPAPORT, S. and ROSCOE, C. The effect of salicylates on the electrolyte structure of the blood plasma. ii. The action of therapeutic doses of sodium salicylate and acetylsalicylic acid in man. *J. Clin. Investigation*, 24: 770, 1945.
19. ALBRIGHT, F. and BAUER, W. The action of sodium chloride, ammonium chloride and sodium bicarbonate on the total acid-base balance of a case of chronic nephritis with edema. *J. Clin. Investigation*, 7: 465, 1929.
20. LESTER, D., GEORGIO, L. and GREENBERG, L. A. The fate of acetylsalicylic acid. *J. Pharmacol. & Exper. Therap.*, 87: 329, 1946.
21. COOMBS, F. S., WARREN, H. A. and HIGLEY, C. S. Toxicity of salicylates. *J. Lab. & Clin. Med.*, 30: 378, 1943.
22. RYDER, H. W., SHAVER, M. and FERRIS, E. B., JR. Salicylism accompanied by respiratory alkalosis and toxic encephalopathy. *New England J. Med.*, 232: 617, 1945.
23. RAPAPORT, A. and GUEST, G. M. The effect of salicylates on the electrolyte structure of the blood plasma. i. Respiratory alkalosis in monkeys and dogs after sodium and methyl salicylates; the influence of hypnotic drugs and sodium bicarbonate on salicylate poisoning. *J. Clin. Investigation*, 24: 759, 1945.
24. BOYLE, M. N., SMULL, K. and WEGRIA, R. The effect of sodium salicylate on the acid-base balance of the blood. *Am. J. Med.*, 3: 31, 1947.
25. ERGANIAN, J. A., FORBES, G. B. and CASE, D. M. Salicylate intoxication in the infant and young child. *J. Pediat.*, 30: 129, 1947.
26. DODD, K., MINOT, A. S. and ARENA, J. M. Salicylate poisoning: an explanation of the more serious manifestations. *Am. J. Dis. Child.*, 53: 1435, 1937.
27. YORK, C. L. and FISCHER, J. H., JR. Plasma-volume determinations in rheumatic subjects during oral salicylate therapy. *New England J. Med.*, 237: 477, 1947.
28. BARNETT, H. L., POWERS, J. R., BENWARD, J. H. and HARTMAN, A. F. Salicylate intoxication in infants and children. *J. Pediat.*, 21: 214, 1942.
29. KRASNOFF, S. O. and BERNSTEIN, M. Acetylsalicylic acid poisoning. *J. A. M. A.*, 135: 712, 1947.

Relative Infectivity of Blood and Cerebrospinal Fluid in Secondary Syphilis*

CHESTER N. FRAZIER, M.D.† and H. C. PIAN, M.D.

Boston, Massachusetts

Tientsin, China

INVASION of the central nervous system of the human host by *Treponema pallidum* is related to the primary dissemination of the organism by the blood. In 1913 Uhlenhuth and Mulzer¹ showed that the blood of patients with primary or secondary syphilis was infectious in the rabbit. Of fifty-five cases of primary or secondary syphilis the blood of forty-three, or 78.2 per cent, when injected into the rabbit's testis in amounts of 2.0 cc. produced syphilitic orchitis.

Within recent years it has been demonstrated that the dissemination of spirochetes in the blood may occur in man even before the appearance of any clinically detectable lesion of syphilis.² In one instance the blood of a donor transmitted a virulent infection to the recipient twenty days before the appearance of a chancre on the penis of the donor and at a time when the serologic tests for syphilis on the donor's blood were negative.³

In 1906 Hoffman first found that the cerebrospinal fluid of a syphilitic man was infectious in the ape.⁴ Since then several studies have shown the presence of *T. pallidum* in the spinal fluid of man during the early stage of syphilis when the fluid was normal on examination by the usual laboratory tests. In three such studies in which the technic of testicular inoculation of the rabbit was used from 15 to 20 per cent of the inoculations gave positive results.⁵⁻⁷ In each case the spinal fluid was apparently normal with respect to cells,

protein, complement fixation and colloidal gold or mastic reaction.

In the last investigation of the problem by Chesney and Kemp the spinal fluids of thirty-four patients were studied.⁸ All patients had one or more clinical signs of early syphilis as well as positive serologic tests on the blood. None had any demonstrable abnormality of the spinal fluid nor did they have any physical sign of neurologic disease. The duration of infection was from three to six months, and secondary manifestations of the disease had been present for from one day to ten weeks. Nine of the patients were white and twenty-five were Negroes; eighteen were males and sixteen were females.

Positive animal inoculations were obtained with the spinal fluid of five, or 14.7 per cent, of the thirty-four patients. Only fluids with cell counts below 9 per cu. mm. were used. All other tests were negative, including complement fixation which was made with 1.0 cc. of spinal fluid. From 0.75 to 3.0 cc. of fluid were used for the inoculation of each rabbit. There was no observable relation between the occurrence of positive inoculations and any particular type of secondary clinical phenomenon of the disease.

As dissemination of the organisms by the blood takes place very soon after infection it must be assumed that invasion of the central nervous system likewise occurs early in the infection. It is obvious that once *T. pallidum* enters the blood stream it neces-

* From the Department of Dermatology and Syphilology, University of Texas, Galveston, Texas, and the Department of Medicine, Peiping Union Medical College, Peiping, China.

† Presently at The Department of Dermatology, Harvard University, Massachusetts General Hospital, Boston, Mass.

sarily is carried to the brain and spinal cord and to the meninges. Just how soon and with what frequency the organisms leave the blood to become localized in the extravascular tissues of the nervous system is unknown. Some indication of this may be obtained by the frequency with which *T. pallidum* is present in the cerebrospinal fluid concurrently with its presence in the blood stream early in the disease. It is with this aspect of the problem that we are concerned.

The study which this paper reports was made in Peiping, China, on Chinese patients observed at the Peiping Union Medical College during the years from 1933 to 1941 inclusive. There was a total of fifty patients; however, the animals inoculated with material from four of the patients were casualties of war and no information concerning them is available. This leaves to be described the results of the study on the blood and spinal fluid of forty-six patients, of whom thirty-eight were males and eight were females.

At the time the inoculations were made all patients presented active signs of secondary syphilis and thirteen also had a primary chancre. There were localizations of disease in the integumentary system in forty-four patients and in the skeletal system in fourteen patients. One patient also had iridocyclitis and another had laryngitis. In no case was there any sign of neurologic disease. The complement fixation (Kolmer) and flocculation (Kahn) tests were positive in all patients. In twenty-nine cases dark field examination of cutaneous lesions was positive for *T. pallidum*. In the remaining patients the lesions were not suitable for dark field examination or no organisms could be found.

Forty patients had received no treatment for syphilis. There were six who had been treated at the time of the chancre with from one to three injections of neoarsphenamine. Subsequently, at intervals of from two to sixteen months all six patients developed a clinical relapse in the integumentary system and, in addition, three patients also had le-

sions of the skeletal structures and one had an iridocyclitis. Four of the six patients had minimal abnormalities of the spinal fluid but no anatomic sign of neural disease. All the clinical relapses were in the males. Virulent organisms were isolated from the blood of each patient with clinical relapse and from the spinal fluid of two patients, each with minimal abnormalities of the fluid.

METHOD OF INOCULATION

For the purpose of isolating *T. pallidum* from the blood and spinal fluid the following method was employed: Venous blood was withdrawn from each patient and immediately 1.0 cc. of blood was injected into each testis of two rabbits. In like manner and in the same amount two rabbits were inoculated with spinal fluid. The inoculated animals were observed at frequent intervals of time, never less than once a week, for ninety days or until signs of orchitis developed. Upon the appearance of orchitis material aspirated from the testis was examined for the presence of *T. pallidum* by dark field illumination. An inoculation was considered positive only when treponemes were found by this technic.

When no organisms could be demonstrated microscopically in the enlarged testis, the testis was removed aseptically, emulsified in a sterile isotonic solution of sodium chloride and 1.0 cc. of the emulsion injected into one testis of each of two rabbits. These animals were observed for at least ninety days before being discarded as normal.

In the event that no orchitis developed after a period of ninety days in the animals originally inoculated with blood or spinal fluid, both popliteal lymph nodes were removed aseptically under ether anesthesia and emulsified in sterile isotonic sodium chloride solution. The entire emulsion was divided and one-half was injected into one testis in each of two rabbits. These animals were in turn observed for at least ninety days or until orchitis developed.

In two instances in which animals of the first transfer developed doubtful evidence of syphilis the involved testis was removed and emulsified and 1.0 cc. of the emulsion injected into a testis of each of another two rabbits.

When the animals inoculated with blood or spinal fluid failed to develop orchitis, the chances

of demonstrating organisms by transfer of tissues were small. In fourteen cases in which either testis or lymph node was transferred from rabbits inoculated with blood only two resulted in establishing a demonstrable infection in the rabbit. Of thirty-seven transfers from rabbits

TABLE I
PERIOD OF INCUBATION OF SYPHILIS IN RABBITS INOCULATED
WITH BLOOD OR SPINAL FLUID

Incubation Period, Days	Animals Infected Inoculum	
	Blood No.	Spinal Fluid No.
30-39	1	0
40-49	10	0
50-59	23	1
60-69	10	4
70-79	4	1
80-89	1	1
90-99	1	0
Total	50	7

inoculated with spinal fluid and failing infection only three tissue transfers gave positive results. In one of these cases organisms were observed only after the second transfer of testicular material. The animal of the original inoculation had developed orchitis from which no *T. pallidum* could be found on dark field examination.

RESULTS OF INOCULATIONS

Infectivity of Blood. The blood from forty-six patients was tested for infectivity. Thirty-five, or 76.1 per cent, of the inoculations produced an infection in rabbits. The original inoculation gave positive results in thirty-three cases. The period of incubation of the disease in these animals is shown in Table I.

Positive inoculations were equally distributed between male and female patients. All patients in clinical relapse had infectious blood.

The distribution of positive inoculations with respect to the duration of infection in the patient, as measured from the appearance of the chancre, is given in Table II. The blood of one female patient was in-

fectious in the rabbit ten months following the chancre. In this case condylomatous lesions of the skin had been present for seven months at the time the inoculation was made. In another case, that of a male patient who was in clinical relapse, the blood

TABLE II
DISTRIBUTION OF POSITIVE INOCULATIONS AND ABNORMAL
SPINAL FLUIDS ACCORDING TO THE DURATION
OF SYPHILIS IN THE PATIENT

Duration of Infection, Mo.	Cases No.	Inoculations		Status of Spinal Fluid		
		Blood Positive No.	Spinal Fluid Positive No.	Normal No.	Abnor- mal No.	Bloody No.
1-2	14	10	0	12	2	0
3-4	15	12	4	10	3	2
5-6	5	5	2	3	1	1
7-8	5	4	3	3	2	0
9-10	1	1	0	1	0	0
11-12	1	0	0	1	0	0
13-	1	1	0	1	0	0
Unknown	4	2	0	4	0	0
Total	46	35	9	35	8	3

was infectious thirty-six months following appearance of the chancre and sixteen months after administration of three doses of neoarsphenamine. The spinal fluid of the two patients was normal and did not infect any rabbits. There were six patients with dark field positive lesions of the skin whose blood did not transmit syphilis.

Infectivity of Cerebrospinal Fluid. The spinal fluids of forty-six patients were transferred to the testes of rabbits. There were nine, or 19.6 per cent, positive inoculations all from the fluids of male patients. In seven instances the animals directly inoculated with spinal fluid developed syphilis in from fifty-six to eighty-two days after the inoculation. (Table I.)

Of the forty-six spinal fluids which were examined thirty-five were normal to routine laboratory tests, including the cell count, protein content, and complement fixation and colloidal mastic reactions. The remainder showed minimal abnormalities in the number of cells and in the content of protein except that three fluids also gave a positive colloidal mastic reaction and one a weakly positive complement fixation reac-

tion (2 plus in 0.5 cc. of fluid). Cell counts above 10 per cu. mm. with or without an increase of protein or above 5 per cu. mm. with an increase of protein were considered abnormal. Five of the normal and four of the abnormal spinal fluids produced syphi-

TABLE III
DISTRIBUTION OF POSITIVE INOCULATIONS AND ABNORMAL SPINAL FLUIDS ACCORDING TO DURATION OF SECONDARY MANIFESTATIONS OF SYPHILIS IN PATIENTS

Duration of Secondary Lesions Wk.	Cases No.	Inoculations		Status of Spinal Fluid		
		Blood Positive No.	Spinal Fluid Positive No.	Normal No.	Abnormal No.	Bloody No.
1- 2	15	11	2	13	2	0
3- 4	9	7	0	5	3	1
5- 6	2	2	1	2	0	0
7- 8	13	9	4	7	4	2
9-10	0	0	0	0	0	0
11-12	2	2	2	1	1	0
13-14	0	0	0	0	0	0
15-16	1	1	0	1	0	0
17-18	0	0	0	0	0	0
19-26	0	0	0	0	0	0
27-28	1	1	0	1	0	0
29-	1	0	0	1	0	0
Unknown	2	2	0	1	1	0
Total	46	35	9	32	11	3

litic orchitis in rabbits. Among the infectious abnormal fluids was the one showing the greatest deviation from normal.

There was no significant correlation between spinal fluids which were infectious for animals and any particular kind of clinical lesion. The nearest approach to such a relationship was in the patients with alopecia. There were ten cases of alopecia among the forty-six patients in the series. Four of the ten patients showing a loss of hair had infectious spinal fluids. In other words, 40 per cent of patients with alopecia and 13.8 per cent of those with no alopecia had fluids which established an infection in rabbits. The difference of 26.2 per cent, however, is not statistically significant, being within the range of sampling error ($\frac{x}{\sigma} = 1.59$).

There has been one previous report on a study of the cerebrospinal fluid in syphilitic Chinese patients. The study was made dur-

ing 1931 to 1932 by Pearce, Hu and Mu at the Peiping Union Medical College.⁹ It is of interest to observe that in none of forty patients who were studied was the spinal fluid infectious in rabbits. Included in the number examined were ten patients with early active manifestations of syphilis who had never been treated for this disease. All had normal spinal fluids. There were also five patients in neurorelapse, three of whom showed an elevated cell count in the spinal fluid. The technic of inoculation, the size of the inoculum and the period over which the animals were observed conformed to the practice in the present study. Both studies were made in the same laboratory. On the basis of our experience one might have expected to find that two or three of the spinal fluids were infectious.

Relative Infectivity of Blood and Spinal Fluid.
From the results of the inoculations it is apparent that infection of the blood in early syphilis does not indicate infection of the spinal fluid. However, infection of the spinal fluid is accompanied by infection of the blood. At least this was true of all patients in this study who had infectious spinal fluids.

It is not to be assumed that the results of inoculation are absolute in their indication of the presence of organisms in either the blood or the spinal fluid. The relative probability of infectivity of the blood and spinal fluid is unknown. Under optimal conditions one is inclined to believe that there are probably more treponemes per unit volume in the blood than in the spinal fluid. The infectivity of these tissues in any case would depend primarily upon the number of organisms present and upon the susceptibility of the rabbit to the first inoculation with organisms unaccustomed to the new host. It might be suspected that the blood of all patients in the active secondary stage of syphilis carries spirochetes although it is possible that the period of greatest infectivity precedes the appearance of metastatic lesions.

If it is assumed that the blood of patients whose infection is not over two months'

duration contains a reasonable number of organisms and is infectious, the blood of all fourteen patients in this study in this period of the disease should have produced syphilis in the inoculated rabbits. As it was only

number of positive inoculations would be twelve, or 26 per cent, of all the tested fluids. This theoretical figure may not be too inaccurate since there were three fluids with minimal abnormalities in the number

TABLE IV

SUMMARY OF CLINICAL AND LABORATORY DATA ON PATIENTS WITH SECONDARY SYPHILIS WHOSE BLOOD AND SPINAL FLUID WERE TESTED FOR INFECTIVITY IN RABBITS

Case No.	Sex	Age Yr.	Duration of Infection Mo.	Duration of Secondary Lesions Wk.	Localization of Lesions			Dark Field Examination	Previous Treatment Arsenical Injections No.	Blood	Serology Spinal Fluid				Animal Inoculation	
					Skin	Hair	Bone				Cells cu.-mm.	Protein	WaR 0.5 cc.	C.M.-R.	Blood	Spinal Fluid
1	M	32	3	2	+	+	-	+	-	+	2	-	-	-	+	+
2	M	30	8	8	+	+	+	+	-	+	34	-	-	+	+	+
3	M	19	4	12	+	-	-	+	-	+	0	-	-	-	+	+
4	M	20	8	12	+	+	-	+	2 (8 mo.)	+	8	+	-	-	+	+
5	M	25	7	8	+	+	+	+	-	+	4	-	-	-	+	+
6	M	43	3	8	+	-	-	+	-	+	12	-	-	-	+	+
7	M	27	5	2	+	-	-	N.E.	-	+	6	-	-	-	+	+
8	M	31	6	8	+	-	-	N.E.	1 (5 mo.)	+	16	+	-	+	+	+
9	M	32	3	6	+	-	+	+	-	+	4	+	-	-	+	+
10	M	31	1	1	+	-	-	+	-	+	2	-	-	-	+	-
11	M	33	36	8	+	+	-	+	3 (16 mo.)	+	4	-	-	-	+	-
12	M	20	3	2	+	-	-	+	-	+	2	-	+	+	+	-
13	M	22	6	2	+	-	-	-	-	+	4	-	-	-	+	-
14	M	46	6	8	+	-	-	+	-	+		Bloody	+	-
15	M	23	2	?	+	-	-	N.E.	-	+	1	-	-	-	+	-
16	F	20	1½	2	+	-	-	+	-	+	2	-	-	-	+	-
17	M	57	2	1	+	-	-	+	-	+	1	-	-	-	+	-
18	M	32	2½	2	+	-	-	+	-	+	4	-	-	-	+	-
19	M	32	3	3	+	-	+	N.E.	1 (2 mo.)	+	4	+	-	-	+	-
20	M	21	3	4	+	-	+	+	1 (2 mo.)	+		Bloody	+	-
21	M	26	3	3	+	-	+	+	2 (2 mo.)	+	6	+	-	-	+	-
22	M	24	6	4	+	+	-	+	-	+	6	+	-	-	+	-
23	M	26	2	2	+	-	+	-	-	+	4	+	-	-	+	-
24	M	13	5	12	+	+	-	+	-	+	0	+	-	-	+	-
25	M	29	3	2	+	-	+	N.E.	-	+	7	-	-	-	+	-
26	F	20	?	8	+	-	-	+	-	+	0	-	-	-	+	-
27	M	26	2	4	+	-	-	+	-	+	9	-	-	-	+	-
28	F	36	7	4	+	-	-	+	-	+	21	-	-	-	+	-
29	F	51	4	8	+	-	+	+	-	+	14	-	-	-	+	-
30	M	26	3	6	+	-	-	+	-	+	2	-	-	-	+	-
31	M	36	1	?	+	-	-	N.E.	-	+	4	+	-	+	+	-
32	M	27	4	4	+	-	+	N.E.	-	+	0	-	-	-	+	-
33	F	35	10	28	+	-	-	+	-	+	4	-	-	-	+	-
34	F	17	?	8	+	-	-	+	-	+	0	-	-	-	+	-
35	M	31	1	2	+	-	-	-	-	+	0	-	-	-	+	-
36	M	16	2	4	+	+	-	+	-	+	2	-	-	-	-	-
37	M	19	4	8	+	+	-	-	-	+		Bloody	-	-
38	M	20	3	8	+	+	+	+	-	+	4	+	N.D.	N.D.	-	-
39	M	25	2	4	+	-	+	+	-	+	8	+	N.D.	N.D.	-	-
40	F	20	?	7	-	-	+	N.E.	-	+	4	-	N.D.	N.D.	-	-
41	M	22	2	2	-	-	-	+	-	+	6	-	-	-	-	-
42	M	25	1	1	+	-	-	-	-	+	8	+	-	-	-	-
43	M	29	4	2	+	-	+	-	-	+	4	-	-	-	-	-
44	M	27	8	2	-	-	+	N.E.	-	+	4	-	-	-	-	-
45	F	17	?	8	+	-	-	+	-	+	10	-	-	-	-	-
46	M	22	12	44	+	-	-	+	-	+	0	-	-	-	-	-

WaR = Wassermann reaction (Kolmer Technic) with 0.5 cc. of spinal fluid. C.M.R. = Colloidal gum mastic reaction.

N.E. = Not examined. N.D. = No data. Under "Previous Treatment" the figures in parentheses show the number of months elapsing between treatment and animal inoculation.

ten of the specimens did so. This would suggest that the experimental error was about 25 to 30 per cent. Assuming further that the same error would apply to the infectivity of the spinal fluid, the expected

of cells and in the content of protein that did not infect rabbits.

This study offers no evidence as to the time after infection when invasion of the spinal fluid occurs. It is of interest, however,

tion (2 plus in 0.5 cc. of fluid). Cell counts above 10 per cu. mm. with or without an increase of protein or above 5 per cu. mm. with an increase of protein were considered abnormal. Five of the normal and four of the abnormal spinal fluids produced syphi-

TABLE III
DISTRIBUTION OF POSITIVE INOCULATIONS AND ABNORMAL SPINAL FLUIDS ACCORDING TO DURATION OF SECONDARY MANIFESTATIONS OF SYPHILIS IN PATIENTS

Duration of Secondary Lesions Wk.	Cases No.	Inoculations		Status of Spinal Fluid		
		Blood Positive No.	Spinal Fluid Positive No.	Normal No.	Abnormal No.	Bloody No.
1- 2	15	11	2	13	2	0
3- 4	9	7	0	5	3	1
5- 6	2	2	1	2	0	0
7- 8	13	9	4	7	4	2
9-10	0	0	0	0	0	0
11-12	2	2	2	1	1	0
13-14	0	0	0	0	0	0
15-16	1	1	0	1	0	0
17-18	0	0	0	0	0	0
19-26	0	0	0	0	0	0
27-28	1	1	0	1	0	0
29-	1	0	0	1	0	0
Unknown	2	2	0	1	1	0
Total	46	35	9	32	11	3

litic orchitis in rabbits. Among the infectious abnormal fluids was the one showing the greatest deviation from normal.

There was no significant correlation between spinal fluids which were infectious for animals and any particular kind of clinical lesion. The nearest approach to such a relationship was in the patients with alopecia. There were ten cases of alopecia among the forty-six patients in the series. Four of the ten patients showing a loss of hair had infectious spinal fluids. In other words, 40 per cent of patients with alopecia and 13.8 per cent of those with no alopecia had fluids which established an infection in rabbits. The difference of 26.2 per cent, however, is not statistically significant, being within the range of sampling error ($\frac{x}{\sigma} = 1.59$).

There has been one previous report on a study of the cerebrospinal fluid in syphilitic Chinese patients. The study was made dur-

ing 1931 to 1932 by Pearce, Hu and Mu at the Peiping Union Medical College.⁹ It is of interest to observe that in none of forty patients who were studied was the spinal fluid infectious in rabbits. Included in the number examined were ten patients with early active manifestations of syphilis who had never been treated for this disease. All had normal spinal fluids. There were also five patients in neurorelapse, three of whom showed an elevated cell count in the spinal fluid. The technic of inoculation, the size of the inoculum and the period over which the animals were observed conformed to the practice in the present study. Both studies were made in the same laboratory. On the basis of our experience one might have expected to find that two or three of the spinal fluids were infectious.

Relative Infectivity of Blood and Spinal Fluid. From the results of the inoculations it is apparent that infection of the blood in early syphilis does not indicate infection of the spinal fluid. However, infection of the spinal fluid is accompanied by infection of the blood. At least this was true of all patients in this study who had infectious spinal fluids.

It is not to be assumed that the results of inoculation are absolute in their indication of the presence of organisms in either the blood or the spinal fluid. The relative probability of infectivity of the blood and spinal fluid is unknown. Under optimal conditions one is inclined to believe that there are probably more treponemes per unit volume in the blood than in the spinal fluid. The infectivity of these tissues in any case would depend primarily upon the number of organisms present and upon the susceptibility of the rabbit to the first inoculation with organisms unaccustomed to the new host. It might be suspected that the blood of all patients in the active secondary stage of syphilis carries spirochetes although it is possible that the period of greatest infectivity precedes the appearance of metastatic lesions.

If it is assumed that the blood of patients whose infection is not over two months'

duration contains a reasonable number of organisms and is infectious, the blood of all fourteen patients in this study in this period of the disease should have produced syphilis in the inoculated rabbits. As it was only

number of positive inoculations would be twelve, or 26 per cent, of all the tested fluids. This theoretical figure may not be too inaccurate since there were three fluids with minimal abnormalities in the number

TABLE IV

SUMMARY OF CLINICAL AND LABORATORY DATA ON PATIENTS WITH SECONDARY SYPHILIS WHOSE BLOOD AND SPINAL FLUID WERE TESTED FOR INFECTIVITY IN RABBITS

Case No.	Sex	Age Yr.	Duration of Infection Mo.	Duration of Secondary Lesions Wk.	Localization of Lesions			Dark Field Examination	Previous Treatment Arsenical Injections No.	Blood	Serology Spinal Fluid				Animal Inoculation	
					Skin	Hair	Bone				Cells cu.-mm.	Protein	WaR 0.5 cc.	C.M.R.	Blood	Spinal Fluid
1	M	32	3	2	+	+	-	+	-	+	2	-	-	-	+	+
2	M	30	8	8	+	+	+	+	-	+	34	-	-	+	+	+
3	M	19	4	12	+	-	-	+	-	+	0	-	-	-	+	+
4	M	20	8	12	+	+	-	+	2 (8 mo.)	+	8	+	-	-	+	+
5	M	25	7	8	+	+	+	+	-	+	4	-	-	-	+	+
6	M	43	3	8	+	-	-	-	-	+	12	-	-	-	+	+
7	M	27	5	2	+	-	-	N.E.	-	+	6	-	-	-	+	+
8	M	31	6	8	+	-	-	N.E.	1 (5 mo.)	+	16	+	-	+	+	+
9	M	32	3	6	+	-	+	+	-	+	4	+	-	-	+	+
10	M	31	1	1	+	-	-	+	-	+	2	-	-	-	+	-
11	M	33	36	8	+	+	-	+	3 (16 mo.)	+	4	-	-	-	+	-
12	M	20	3	2	+	-	-	+	-	+	2	-	+	+	+	-
13	M	22	6	2	+	-	-	-	-	+	4	-	-	-	+	-
14	M	46	6	8	+	-	-	+	-	+		Bloody	+	-
15	M	23	2	?	+	-	-	N.E.	-	+	1	-	-	-	+	-
16	F	20	1½	2	+	-	-	+	-	+	2	-	-	-	+	-
17	M	57	2	1	+	-	-	+	-	+	1	-	-	-	+	-
18	M	32	2½	2	+	-	-	+	-	+	4	-	-	-	+	-
19	M	32	3	3	+	-	+	N.E.	1 (2 mo.)	+	4	+	-	-	+	-
20	M	21	3	4	+	-	+	+	1 (2 mo.)	+		Bloody	+	-
21	M	26	3	3	+	-	+	+	2 (2 mo.)	+	6	+	-	-	+	-
22	M	24	6	4	+	+	-	+	-	+	6	-	-	-	+	-
23	M	26	2	2	+	-	+	-	-	+	4	-	-	-	+	-
24	M	13	5	12	+	+	-	+	-	+	0	+	-	-	+	-
25	M	29	3	2	+	-	+	N.E.	-	+	7	-	-	-	+	-
26	F	20	?	8	+	-	-	+	-	+	0	-	-	-	+	-
27	M	26	2	4	+	-	-	+	-	+	9	-	-	-	+	-
28	F	36	7	4	+	-	-	+	-	+	21	-	-	-	+	-
29	F	51	4	8	+	-	+	+	-	+	14	-	-	-	+	-
30	M	26	3	6	+	-	-	+	-	+	2	-	-	-	+	-
31	M	36	1	?	+	-	-	N.E.	-	+	4	+	-	+	+	-
32	M	27	4	4	+	-	+	N.E.	-	+	0	-	-	-	+	-
33	F	35	10	28	+	-	-	+	-	+	4	-	-	-	+	-
34	F	17	?	8	+	-	-	+	-	+	0	-	-	-	+	-
35	M	31	1	2	+	-	-	-	-	+	0	-	-	-	+	-
36	M	16	2	4	+	+	-	+	-	+	2	-	-	-	-	-
37	M	19	4	8	+	+	-	+	-	+		Bloody	-	-
38	M	20	3	8	+	+	+	+	-	+	4	+	-	-	-	-
39	M	25	2	4	+	-	+	+	-	+	8	+	N.D.	N.D.	-	-
40	F	20	?	7	-	-	+	N.E.	-	+	4	-	N.D.	N.D.	-	-
41	M	22	2	2	-	-	-	+	-	+	6	-	-	-	-	-
42	M	25	1	1	+	-	-	-	-	+	8	+	-	-	-	-
43	M	29	4	2	+	-	+	-	-	+	4	-	-	-	-	-
44	M	27	8	2	-	-	+	N.E.	-	+	4	-	-	-	-	-
45	F	17	?	8	+	-	-	+	-	+	10	-	-	-	-	-
46	M	22	12	44	+	-	-	+	-	+	0	-	-	-	-	-

WaR = Wassermann reaction (Kolmer Technic) with 0.5 cc. of spinal fluid. C.M.R. = Colloidal gum mastic reaction.

N.E. = Not examined. N.D. = No data. Under "Previous Treatment" the figures in parentheses show the number of months elapsing between treatment and animal inoculation.

ten of the specimens did so. This would suggest that the experimental error was about 25 to 30 per cent. Assuming further that the same error would apply to the infectivity of the spinal fluid, the expected

of cells and in the content of protein that did not infect rabbits.

This study offers no evidence as to the time after infection when invasion of the spinal fluid occurs. It is of interest, however,

that none of the fourteen patients with infections of less than three months' duration had spinal fluid which was infectious in the rabbit while four of fifteen patients with infections of from three to four months' duration had infectious fluids.

It is to be observed in Table III that in two patients with secondary manifestations of not over two weeks' duration the spinal fluid was found to contain virulent organisms.

SUMMARY

The blood and cerebrospinal fluid of forty-six Chinese patients in the active secondary stage of syphilis were inoculated into rabbits. The blood proved to be infectious in thirty-five, or 76.1 per cent, and the spinal fluid in nine, or 19.6 per cent, of the cases. There was no correlation between a particular clinical lesion and infectivity of the spinal fluid although the frequency of positive inoculations in patients with alopecia approached statistical significance. (Table IV.)

No organisms were isolated from the spinal fluid of patients whose infections were of less than three months' duration. All

patients with infectious spinal fluids also had virulent organisms in their blood.

REFERENCES

1. UHLENHUTH, P. and MULZER, P. Weitere Mitteilungen über die Infektiosität des Blutes und anderer Körperflüssigkeiten syphilitischer Menschen für das Kaninchen. *Berl. klin. Wchnschr.*, 50: 769, 1913.
2. PIAN, H. C. and FRAZIER, C. N. Transfusion syphilis with widespread osteomyelitis and cutaneous lesions of an erythema multiforme type. *Chinese M. J.*, 57: 301, 1940.
3. FRAZIER, C. N. and PIAN, H. C. Isolation of *Treponema pallidum* from the blood during the primary incubation period of human syphilis. *Chinese M. J.*, 56: 441, 1939.
4. HOFFMAN, E. Mitteilungen und Demonstrationen über experimentelle Syphilis, *Spirochaeta pallida* und andere Spirochaetenarten. *Dermat. Ztschr.*, 13: 561, 1906.
5. STEINER, G. Zur Erzeugung und Histopathologie der experimentellen Syphilis des Zentralnervensystems beim Kaninchen. *Neurol. Centralbl.*, 33: 546, 1914.
6. ARTZ, L. and KERL, W. Ueber experimentelle Kaninchensyphilis und ihre praktische Bedeutung. *Wien. klin. Wchnschr.*, 27: 785, 1914.
7. FRUHWALD, R. Ueber die Infektiosität des Liquor cerebrospinalis bei Syphilis. *Berl. klin. Wchnschr.*, 53: 9, 1916.
8. CHESNEY, A. M. and KEMP, J. E. Incidence of *Spirochaeta pallida* in cerebrospinal fluid during early stage of syphilis. *J. A. M. A.*, 83: 1725, 1924.
9. PEARCE, L., HU, C. K. and MU, J. W. Failure to demonstrate *Spirochaeta pallida* in cerebrospinal fluid of syphilitic Chinese patients. *Arch. Dermat. & Syph.*, 34: 639, 1936.

Penicillin in Oil and Beeswax in the Treatment of Syphilis in Clinic Patients^{*}

HENRY EISENBERG, M.D. and FREDERICK PLOTKE, M.D.

Chicago, Illinois

THE successful treatment of syphilis within the last thirty-five years has been greatly hampered by the fact that the various drugs used had to be given over a period of many months in order to be effective. A great proportion of patients lapsed from this type of prolonged treatment before any therapeutic effects were ever obtained. In Kampmeier's book, "Essentials of Syphilology," Alvin E. Keller states that "only 20 to 30 per cent of all patients receiving anti-syphilitic treatment received as many as 20 injections of an arsenical preparation and 20 injections of a heavy metal." This fact has been confirmed by various other authors.

Ever since penicillin was accepted as an efficient and the least toxic of all anti-syphilitic agents, it has been the aim of syphilologists to develop an effective wholly ambulatory treatment schedule. A step forward in this direction was made when Romansky's formula became available, ensuring therapeutic levels in the vast majority of patients for at least a twenty-four-hour period following a single injection of 300,000 units of POB. This method of administering penicillin has proved to be of considerable value, particularly to communities where intensive treatment centers or other public health facilities are not readily available.

The Clinic Section of the Chicago Venereal Disease Control Program undertook to determine the cooperativeness of clinic patients in completing a short term method of treatment with penicillin in oil and beeswax on an ambulatory basis. The

study was begun in February, 1947, and was first intended to include only untreated or insufficiently treated late latent syphilis cases. However, soon after the study was started other types of syphilis such as early latent syphilis, asymptomatic and symptomatic neurosyphilis without frank psychosis, cardiovascular syphilis, congenital syphilis, syphilis in pregnancy and even a number of early infectious cases were included in this study. The latter group consisted of patients who were unable for various reasons to enter the hospital for intensive therapy. All patients placed on penicillin therapy from February, 1947, to February, 1948, are included in this report. This group of patients constitutes approximately 30 per cent of all types of syphilis cases diagnosed by the Chicago Health Department clinics.

In the beginning of the study of late latent syphilis, patients who either had no treatment or less than twenty arsenicals and twenty bismuth injections were included in the series. After a personal interview with the caseworker, who pointed out the advantages of this new treatment schedule and the importance of regular attendance, the patients received daily injections of 450,000 units of penicillin in oil and beeswax over a period of ten treatment days (omitting Saturdays and Sundays), a total of 4,500,000 units. Exceptions: (1) the treatment schedule for group 2 and group 3 spinal fluid changes in neurosyphilis, as defined by J. E. Moore in his book, "The Modern Treatment of Syphilis" (1947 edition), was increased to fifteen treatment days, or 6,750,000 units and (2) patients

^{*} From the Venereal Disease Control Program of the Chicago Health Department, in cooperation with the United States Public Health Service.

with cardiovascular syphilis were treated with 100,000 units per day for three days, increased to 200,000 units on the fourth and fifth treatment days and to 300,000 units from the sixth to the fifteenth day.

the clinics are of the late latent type. Neurosyphilis is the next largest group in this study with 24.9 per cent. This group constitutes only 3 per cent of the total syphilitic cases diagnosed during 1947. It is of interest to

TABLE I
SYPHILIS PATIENTS UNDER TREATMENT WITH PENICILLIN IN OIL AND BEESWAX

Diagnosis	Total		Male				Female			
	No.	Per Cent	White	Color- ed	Total	Per Cent	White	Color- ed	Total	Per Cent
Primary syphilis.....	4	0.4	2	2	4	0.8	0.0
Secondary syphilis.....	2	0.2	...	1	1	0.2	..	1	1	0.2
Early latent syphilis.....	12	1.2	2	3	5	1.2	1	6	7	1.4
Late latent syphilis.....	596	59.6	54	228	282	58.4	27	287	314	60.7
Neurosyphilis.....	249	24.9	58	108	166	34.4	35	48	83	16.0
Cardiovascular syphilis.....	12	1.2	1	5	6	1.2	..	6	6	1.2
Congenital syphilis.....	32	3.2	2	17	19	3.9	1	12	13	2.5
*Syphilis complicated by pregnancy.....	93	9.3	1	92	93	18.0
Total	1000	100.0	119	364	483	100.0	65	452	517	100.0

* Early latent syphilis.....	50
Late latent syphilis.....	34
Cardiovascular syphilis.....	1
Congenital syphilis.....	8
Total.....	93

All patients were instructed to return daily for their prescribed treatment except on Saturdays and Sundays but they were permitted to lapse for two days between treatment days before the lapse was considered permanent. Patients who attended the clinic three or more times a week, completing ten injections within twenty-one days, were considered in this study to have completed their treatment satisfactorily. If a patient lapsed for more than two days between treatment, he was re-instituted on the prescribed treatment schedule.

A statistical tabulation of 1,000 patients so treated with penicillin in oil and beeswax on an ambulatory basis is herewith presented. Table I shows a classification of cases into the various types of syphilis. The largest group constitutes late latent syphilis with 59.6 per cent of all patients although only 23 per cent of all syphilis cases diagnosed in

note that in the group of 1,000 patients there is a slightly larger proportion of female patients, namely, 51.7 per cent, while in the total group of diagnosed syphilis cases we have approximately 47 per cent of female patients. This, however, is not a significant difference.

In both the cases of this study and the total number of syphilis cases diagnosed in the clinics during 1947, approximately 18 per cent were white.

A breakdown in age groups of all patients in this study is shown in Table II. The median age of the syphilis patients treated with POB is thirty-eight years, while the median age of all syphilis patients diagnosed is twenty-five years of age. We find, therefore, that the color and sex rate in this study group and in the total group of patients diagnosed during the study period show no appreciable difference. The dis-

crepancy in the median age between these two groups is explained by selection of the latent syphilis cases for this study.

As shown in Table III, of a total of 1,000 patients 859 or 85.9 per cent completed their prescribed treatment, and 141 patients

In reviewing the charts of those patients who lapsed at one time or another, it was found that the reasons of their lapsing were given as follows: seventeen patients experienced a severe rash, eleven complained of sore hips; among the remaining 185

TABLE II
SYPHILIS PATIENTS TREATED WITH PENICILLIN IN OIL AND BEESWAX

Diagnosis	Age Groups—Years							
	2-9	10-19	20-29	30-39	40-49	50-55	Over 55	Total
Primary syphilis	0	0	3	1	0	0	0	4
Secondary syphilis	0	0	1	1	0	0	0	2
Early latent syphilis	0	1	6	4	1	0	0	12
Late latent syphilis	0	0	90	244	174	63	25	596
Neurosyphilis	0	0	30	65	92	39	23	249
Cardiovascular syphilis	0	0	1	3	4	3	1	12
Congenital syphilis	1	24	6	0	1	0	0	32
Syphilis complicated by pregnancy	0	4	55	33	1	0	0	93
Total (all forms by age groups)	1	29	192	351	273	105	49	1,000

TABLE III
SYPHILIS PATIENTS PLACED UNDER TREATMENT AND COMPLETING PRESCRIBED TREATMENT SCHEDULE, CLASSIFIED ACCORDING TO SEX AND TYPE OF SCHEDULE*

	Total			Ten-day Schedule			Fifteen-day Schedule		
	Placed under R ₁	Completed R ₁	Per Cent Completed R ₁	Placed under R ₁	Completed R ₁	Per Cent Completed R ₁	Placed under R ₁	Completed R ₁	Per Cent Completed R ₁
Male	483	406	84.1	334	281	84.1	149	125	83.9
Female	517	453	87.6	433	386	89.1	84	67	79.8
Total	1,000	859	85.9	767	667	87.0	233	192	82.4

* Includes reinstatements after lapse to first regimen.

discontinued for various reasons. There were 767 patients on the ten-injection-day schedule, of whom 87.0 per cent completed the course and 233 on the fifteen-injection-day regimen, of whom 82.4 per cent finished their prescribed course. Although 141 patients failed to complete treatment, there were 213 patients who lapsed from the first regimen. However, seventy-two of the eighty-eight patients (81.8 per cent) were reinstated and finished a new treatment course.

patients there were sixty patients who gave intercurrent personal or familial illness as the reason for discontinuance of treatment, while 125 patients disappeared without indicating the cause.

SUMMARY AND CONCLUSIONS

1. The clinic attendance of 1,000 syphilitic patients placed on an ambulatory ten- or fifteen-day-treatment schedule of penicillin in oil and beeswax is recorded.

2. Eighty-five and nine-tenths per cent

of all patients completed their prescribed treatment regimen; divided according to the two different treatment schedules employed, 87.0 per cent completed their ten-injection-day regimen and 82.4 per cent completed their fifteen-day schedule.

3. Twenty-eight patients discontinued or lapsed treatment because of local or allergic manifestations and sixty patients failed to complete treatment because of intercurrent illnesses either personal or within their families; 125 patients disap-

peared from observation for unknown reasons.

4. This form of therapy is far superior as regards clinic attendance compared with the 30.0 per cent attendance recorded for long-term chemotherapy.

The authors wish to acknowledge their indebtedness to Dr. Herman N. Bundesen, President of the Chicago Board of Health and to Theodore J. Bauer, Senior Surgeon, U.S.P.H.S., Venereal Disease Control Officer, Chicago Health Department.

Auricular Flutter in Association with Myocardial Infarction*

Its Prognosis and Management

JOHN MARTIN ASKEY, M.D.

Los Angeles, California

AURICULAR flutter is an arrhythmia rarely encountered in association with myocardial infarction. It was found in 3 (1 per cent) of 300 patients reported by Master¹ and in 5 of 208 patients (2.5 per cent) in Rosenbaum and Levine's³ series. Recently Chambers² recorded three instances in one hundred patients with myocardial infarction. Among 1,247 patients studied at the Los Angeles County Hospital it was discovered in nineteen instances (1.5 per cent). In the same group auricular fibrillation was found in eighty-four instances (7.7 per cent). The burden imposed by auricular flutter ordinarily depends upon the concomitant state of the heart itself as well as the nature of the flutter. The faster the ventricular rate and the longer the persistence of the tachycardia, the greater the burden and the greater the hazard. In association with the acute cardiac damage of myocardial infarction, auricular flutter with tachycardia should constitute a serious handicap.

These nineteen cases represent the material used in this study. We were concerned chiefly with the prognostic importance of auricular flutter and its management. We have analyzed this series with these two considerations particularly in mind.

Mortality. Twelve of the nineteen patients (63 per cent) died during the period of hospitalization. The mortality of the whole group of 1,247 patients was 51.5 per cent. Of the twelve patients who died, in

eight the auricular flutter persisted until death, seven with a ventricular rate of 140 or more. (Table I.) The majority (five of the eight) died within twenty-four hours of the onset, with ventricular rates over 140. One died two days, one four days and one

TABLE I
TYPE OF DEATH IN EIGHT PATIENTS WITH AURICULAR FLUTTER AND MYOCARDIAL INFARCTION

Cause of Death	Ventricular Rate	Comments
Acute congestive failure.	150 for 4 days	Previous infarction
Sudden death.....	120 for 2 days	Previous infarct, intraventricular block
Sudden death.....	150 for 1 day	Previous infarct
Sudden death.....	160 for 1 day	Previous infarct, intraventricular block
Acute congestive failure.	140 for 5 days	"Enlarged heart" before
Acute congestive failure.	142 for 1 day	Intraventricular block, angina before attack
Acute left ventricular failure.....	140 for 1 day	
Acute congestive failure.	140 for 1 day	

five days after the onset. Five of the eight deaths were attributed to acute congestive failure, three were sudden deaths presumably due to a fatal ectopic ventricular rhythm. There is little doubt that the persisting rapid ventricular rate was the immediate cause of death in these patients. Among the four patients who died despite a return to normal rhythm the causes of death were as follows: (1) Acute congestive failure. In one patient the ventricular rate had remained at 160 for fourteen days before the return to normal rhythm. The prolonged tachycardia induced death even

*From the Department of Medicine, the University of Southern California Medical School and the Los Angeles County Hospital, Los Angeles, Calif.

though sinus rhythm returned. (2) Sudden death. One patient died suddenly eight days after a return to normal rhythm. The auricular flutter had lasted only one day and was associated with a normal ventricular rate. It probably did not influence the

TABLE II
RESPONSE TO MEDICATION IN AURICULAR FLUTTER
ASSOCIATED WITH MYOCARDIAL INFARCTION

Medication	No. of Patients	No. Returning to Normal Rhythm
No medication	8	5
Digitalis and quinidine	4	2
Digitalis alone	5	2
Quinidine alone	2	2

death. (3) Pneumonitis. One patient died of supposed pneumonia; auricular flutter with a ventricular rate of 120 had lasted two days. This patient had had a previous myocardial infarction three years before. The auricular flutter can be implicated as a contributory cause of death. (4) Myocardial infarction. The fourth patient died of a second infarct. The auricular flutter had occurred twice, disappearing each time within twenty-four hours. It apparently was of negligible importance in the cause of death, merely reflecting the severe cardiac damage. From these data it would appear that auricular flutter was responsible for at least nine of the twelve deaths due to the burden of the associated tachycardia. Death in the other three patients probably would have occurred even if auricular flutter had not been present.

Persistence of the Auricular Flutter. In eight patients arrhythmia persisted; in eleven patients it disappeared.

Correlation of Mortality with Persistence of the Auricular Flutter. All of the eight patients with persistence of the auricular flutter died. Of the eleven patients in whom the arrhythmia disappeared four died (36.3 per cent), seven lived.

Correlation of the Ventricular Rate with Mortality. Of the thirteen patients with ventricular rates of 120 or more eleven died (85.7 per cent). Of the six with a

ventricular rate of 100 or less one died (16.6 per cent).

Correlation of Ventricular Rate with Subsequent Persistence or Disappearance of the Arrhythmia. Only five of the thirteen with ventricular rates over 120 returned to normal rhythm. Of six with ventricular rates below 100 all returned to normal rhythm.

Correlation of Persistence with the Severity of the Heart Disease. Of the eight patients with persistence of arrhythmia five gave a history suggestive of previous infarction. This was confirmed in four necropsies obtained in the eight patients. A sixth patient had had a previously enlarged heart. Six (or 75 per cent) gave, therefore, a history of previous heart trouble. Of the eleven in whom the arrhythmia disappeared only four (33.3 per cent) gave histories of previous cardiovascular disease.

RESPONSE OF AURICULAR FLUTTER TO DIFFERENT TREATMENT

Response of the auricular flutter to varying treatment is shown in Table II. Few deductions are justified from the data because dosage of the drugs was not optimum. Among the five patients given both digitalis and quinidine the dosage varied considerably and probably was not adequate for both of the drugs. In only three patients was the dosage sufficient to justify an analysis of the response. Of the five patients given digitalis alone in only two was the dosage adequate. In only one of these patients did the rhythm return to normal. In the two patients given quinidine alone the return to normal rhythm might easily have been spontaneous. The dosage of quinidine was not optimum.

CASE REPORTS

CASE No. 707069. A man, aged seventy-five with no preceding cardiovascular history, had an attack of chest pain March 5, 1940. An electrocardiogram March 6, 1940, revealed the pattern of anterior infarction. The following day auricular flutter with a ventricular rate of 160 developed. Digitalis (powdered leaf pills) was given in successive daily doses of $13\frac{1}{2}$ gr.,

6 gr., 3 gr. and then $1\frac{1}{2}$ gr. daily. There was no change in the auricular flutter for eleven days, from March 7, 1940 to March 18, 1940. Quinidine was then given in doses varying from 40 to 54 gr. daily. Sinus rhythm returned four days later, on March 22, 1940, but the patient died the same day of acute left ventricular failure.

This illustrates the difficulty at times of affecting auricular flutter at all. It illustrates also the difficulty of affecting some patients quickly even with large doses of digitalis and quinidine. This patient had a ventricular rate of 160 from March 7, 1940 to March 21, 1940 (fourteen days). Undoubtedly this tachycardia was the cause of death. In retrospect, we could wish that quinidine had been given sooner. Had it been started on the first day the ventricular rate possibly could have been controlled sooner.

CASE No. 819627. A man, aged seventy-two with previous known hypertensive cardiovascular disease, was admitted October 6, 1941, with a history of myocardial infarction occurring three weeks before. The electrocardiogram confirmed this diagnosis and showed auricular flutter, with a ventricular rate of 150 and 2:1 auriculoventricular block. Lanatoside C was given intravenously (4 cc. of cedilanid). Two days later there was normal rhythm. On October 10, 1941, digitalis by mouth, ($1\frac{1}{2}$ gr. of powdered leaf) was started daily and also quinidine in 6-gr. doses four times daily. Five days later, October 15, 1941, despite this medication, impure auricular flutter appeared. Digitalis was increased to $1\frac{1}{2}$ gr. four times daily and quinidine was continued 3 gr. four times daily. The next day normal rhythm returned and continued for one month at which time the patient developed a second infarct with an electrocardiographic pattern of a posterior lesion. He died suddenly the same day. Therapy for the flutter, however, may be considered satisfactory in this case inasmuch as death was not ascribed to the arrhythmia.

Auricular Flutter and Complete Auriculoventricular Block in Association with Myocardial Infarction. The simultaneous occurrence of auricular flutter and complete auriculoventricular block in any heart condition is unusual. (Table III.) Jourdonais and Mosen-

thal⁴ reviewed the twenty-nine reports in the literature of auricular flutter associated with complete auriculoventricular block and recorded another instance. Nearly all patients were middle-aged men with arteriosclerotic heart disease. DeMoura⁵ recently recorded an instance in a thirty year old male with rheumatic heart disease. The flutter and complete block persisted until death. No necropsy was obtained. De Gregorio and Crawford⁶ recorded two more instances, one patient had suffered a recent coronary occlusion. Gray and Greenfield⁷ reported another case but the necropsy revealed no recent infarction. Miller and Perelman⁸ described a patient with myocardial infarction three years before who developed auricular flutter and complete auriculo-ventricular block. Katz⁹ shows a tracing of this condition in his book. We wish to describe a patient in whom auricular flutter and complete auriculoventricular block with the Stokes-Adams syndrome occurred coincident with myocardial infarction.

CASE No. 753017. Mr. H. K., eighty-two years old, was admitted May 29, 1941. He had awakened at 5 A.M. very short of breath but with no pain. Physical examination revealed an old man acutely dyspneic and cyanotic, passing into a state of stupor for a short time and then becoming mentally clear. There were occasional mild convulsive movements. The blood pressure was 100 systolic, 60 diastolic. The heart sounds were weak, irregular, with a rate of 30 to 40. An electrocardiogram taken on two occasions, on May 29, 1941, showed auricular flutter and auriculoventricular dissociation. The patient continued to suffer severe convulsive seizures with bradycardia. At times the heart rate would change suddenly to 100. He was given $\frac{3}{8}$ gr. of ephedrine sulfate every four hours day and night from May 29, 1941 to June 2, 1941, and adrenalin, 10 minims, hypodermically for the acute attacks of Stokes-Adams seizures. On June 2, 1941, normal sinus rhythm had returned. There was no return of auricular flutter or heart block. The further course was uneventful. He was discharged on June 26, 1941. He was seen at the orthopedic clinic for an injured leg on September 16, 1941, and had no medical complaints. The

TABLE III
AURICULAR FLUTTER COMPLICATING MYOCARDIAL INFARCTION; ANALYSIS OF NINETEEN OCCURRENCES AMONG 1,247 PATIENTS WITH MYOCARDIAL INFARCTION

Age	Sex	Evidence of Previous Infarct		Previous Cardiovascular History	Other Arrhythmias or Defects	A-V Block and Ventricular Rate	Days after Attack	Days Auricular Flutter Lasted	Did Sinus Rhythm Return	Type of Death	Did Auricular Flutter Cause Death	Medication		Comment
		History	Necropsy									Digitalis	Quinidine	
61	M	Positive	Recent and old infarct	Edema, orthopnea 1½ yr.	V.P.B.	2-1 Aur. rate, 290 Ven. rate, 150	5	4 (until death)	No	Acute congestive failure	Yes, rapid ven. rate	Only maintenance dose	None	Medication inadequate
72	M	Chest pain	Recent and old infarct	Dyspnea, chest pain 1 yr.	i.v. block	Aur. rate, 240 to 360; Ven. rate, 120	7	2 (until death)	No	Sudden death	Yes	After 24 hours 4 cc. cedilanid i.v., plus 6 doses of oral cedilanid	None	
66	F	Chest pain	Recent and old infarct	Chest pain 3 yr.	0	2-1 Aur. rate, 300 Ven. rate, 150	3	1 (died same day)	No	Sudden death	Yes	1½ gr. for 4 doses	3 gr. then 6 gr. every 2 hr. for 5 doses	Digitalis not adequate; quinidine adequate
46	M	Positive	Recent and old infarct	Chest pain; high blood pressure	0	3-1 Aur. rate, 480 Ven. rate, 160	3	1 (died same day)	No	Sudden death	Yes	None	None	No time to give adequate amount
52	M	None	No necropsy	Enlarged heart	Sinus tachycardia, 110	2-1 Aur. rate, 280 Ven. rate, 140	11 5 wk.	(died 5 days later)	No	Acute congestive failure	Yes	9 gr.	Started after 3 days 6 gr. every hr. for 8 doses	Digitalis not adequate; quinidine started late
34	M	Chest pain 1 yr. before	No necropsy	Chest pain 1 yr. before	i.v. block	2-1 Aur. rate, 290 Ven. rate, 142	2	(Died same day)	No	Acute congestive failure	Yes	None	None	No time to give medication
83	M	None	No necropsy	None	0	2-1 Aur. rate, 280 Ven. rate, 140	9	1 (died next day)	No	Acute congestive failure; ven. fib.	Yes	None	None	Not adequate
68	F	Positive 3 yr. before	No necropsy	High blood pressure 10 yr.; infarct 3 yr. before	Aur. fib.	3-1 Aur. rate, 360 Ven. rate, 120	5 wk.	2 days, then aur. fib. then sinus rhythm	Yes	Pneumonia	No	10½ gr. in 2 days	None	May have been spontaneous
72	M	None	No necropsy	Dyspnea on effort 6 mo; high blood pressure; enlarged heart	i.v. block	2-1 Aur. rate, 280 Ven. rate, 140	21	2 days 1 day	Yes	Second infarct	No	Cedilanid 4 cc. i.v. digitalis 1½ gr. daily orally	3 gr. four times a day	First infarct anterior, second infarct with death posterior (9 wk. later)
57	M	None	No necropsy	None	Aur. fib.	4-1 Aur. rate, 300 Ven. rate, 75	15	1 (died 8 days later)	Yes	Sudden death	No	None	3 gr. for 5 doses	May have been spontaneous

TABLE III (Continued)

Age	Sex	Evidence of Previous Infarct		Previous Cardiovascular History	Other Arrhythmias or Defects	A-V Block and Ventricular Rate	Days after Attack	Days Auricular Flutter Lasted	Did Sinus Rhythm Return	Type of Death	Did Auricular Flutter Cause Death	Medication		Comment
		History	Necropsy									Digitalis	Quinidine	
75	M	None	No necropsy	None	0	Aur. rate, 300 Ven. rate, 160 For 14 days 2-1	2	14	Yes	Acute congestive failure	Yes	24 gr. in 24 hr., then 1½ gr. daily for 10 days	After 10 days 40-54 gr. daily for 4 days	Adequate dosage by usual criteria
48	M	None	Lived 6 mo.	High blood pressure	Aur. fib.	2-1 Aur. rate, 300 Ven. rate, 150	6	1	Yes	Lived 6 mo.	No apparent bad effect	None	None	
55	M	None	Lived	None	A.v. block	Variable Aur. rate, 400 Ven. rate, 80	18	Gone after 19 days	Yes	Lived	No apparent bad effect	None	None	No EKG for 19 days
66	F	None	Lived	None	A.P.B.	2-1 and 3-1 Ven. rate, 145	2	Gone after 9 days	Yes	Lived	No apparent bad effect	None	None	No EKG for 9 days
57	M	None	Lived	Rh. ht. dis.; dyspnea, yr.	0	4-1 Aur. rate, 300 Ven. rate, 75	13	4	Yes	Lived	No, slow ven. rate	28 gr. in 3 days	None	
61	M	None	Lived	None	Sinus tachycardia, 130; transient i.v. block	4-1 Aur. rate, 320 Ven. rate, 85	5	1	Yes	Lived	No, slow ven. rate	None	None	
82	M	None	Lived	None	A.v. block	Complete A.v. block; aur. rate, 220 Ven. rate, 20-50	1	2	Yes	Lived	Lived	None	None	
55	M	None	Lived	Chest pain on exertion	A.P.B.	Variable; aur. rate, 210 Ven. rate, 70	6	1	Yes	Lived	No, slow ven. rate	None	3 gr. three times a day	
51	M	None	Recent infarct	None	0	Aur. rate, 280 Ven. rate, 140	1	1	No	Acute left ven. failure	Yes	4 cc. digilamid i.v.	None	

A.P.T.—auricular paroxysmal tachycardia.

A.P.B.—auricular premature beats.

V.P.B.—ventricular premature beats.

I.v. block—intraventricular block.

Rh. ht. dis.—rheumatic heart disease.

Aur. fib.—auricular fibrillation.

Ven. fib.—ventricular fibrillation.

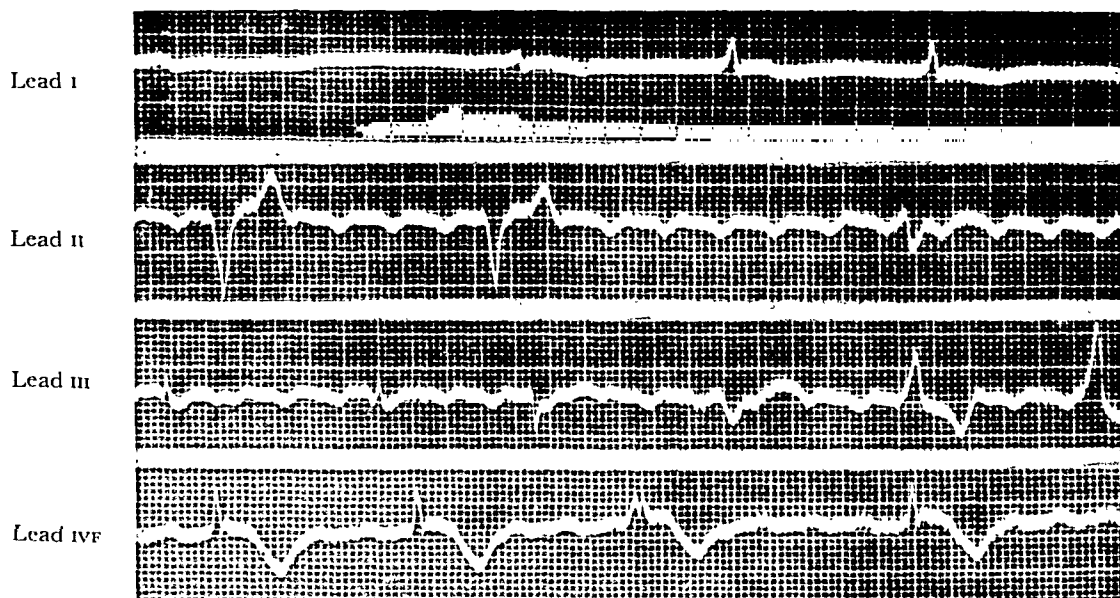


FIG. 1. Auricular flutter May 29, 1941. Complete auriculoventricular block; irregular idioventricular rhythm due to varying foci of ventricular pacemakers; anterior infarction.

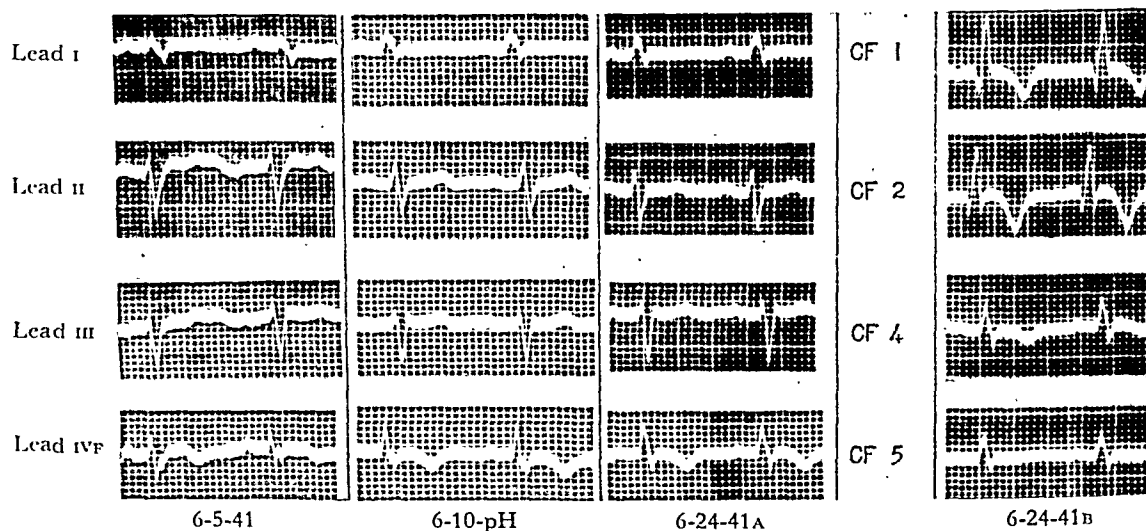


FIG. 2. Serial tracings after return to sinus rhythm; June 5, 1941, sinus rhythm, right bundle branch block; June 10th, sinus rhythm, left bundle branch block with reversal of bundle branch block since previous tracing; T IVF changes progressive; 6-24-41A, sinus rhythm, left bundle branch block; 6-24-41B, T wave inversion most marked in CF₁ and CF₂.

serial electrocardiograms are shown and corroborate the diagnosis of anterior myocardial infarction. (Figs. 1 and 2.)

The occurrence of complete auriculoventricular block and auricular flutter synchronous with an attack of myocardial infarction is extremely rare. Recovery from these complications by a patient eighty-two years old is amazing. The apparent intraventricular block present in the first tracing was not confirmed until the auriculo-

ventricular block was gone and the widened QRS complex persisted. Widened QRS complexes occur commonly in complete auriculoventricular block but are not indicative of associated intraventricular block *per se*. They may indicate merely that the focus for the idioventricular pacemaker is below the bifurcation of the common bundle. Katz⁹ believes a diagnosis of intraventricular block is not justified unless records taken when complete auriculo-

ventricular block is absent show that the condition exists. In the thirty-six records in the literature the QRS complexes were widened in ten instances. An interesting feature in several instances was an apparent reversal at times of the bundle branch block patterns.

AURICULAR FIBRILLATION VERSUS AURICULAR FLUTTER IN MYOCARDIAL INFARCTION

A comparison of the varying effect of auricular fibrillation and auricular flutter as a complication of myocardial infarction is of interest. The two arrhythmias have much in common in their relationship to myocardial infarction, even as they have in relation to other types of heart disease. They usually are a reflection of serious heart damage. If they occur with myocardial infarction, usually they indicate the existence of previous cardiovascular disease. In the group of eighty-four patients with auricular fibrillation discovered in the whole group of 1,247, fifty-eight (62 per cent) gave signs or symptoms of previous cardiovascular disease. In the group of nineteen with auricular flutter there were eleven (58 per cent). In both groups the majority of those in whom the arrhythmia persisted had either a history or necropsy evidence of previous infarction. The relation of the time of onset of the arrhythmia to the time of the attack was interesting and varied in the two arrhythmias. Whereas auricular fibrillation occurred in a large percentage at approximately the same time as the attack (forty-nine of eighty-four patients), auricular flutter occurred after the attack in all patients, in the majority six days or more after the attack.

The difference in the incidence of embolism was interesting but not unexpected. Whereas among those with auricular fibrillation there was a high percentage of pulmonary and systemic embolism, no diagnosis of embolism was made as a complication of auricular flutter. This is in keeping with what is observed in arrhythmias complicating other heart conditions. McMillin and Bellet¹⁰ commented on the

low incidence of embolism accompanying auricular flutter in general and stated that "the weight of evidence indicates that embolism rarely if ever occurs during flutter." The mortality associated with both arrhythmias, if persistent, was very high. Four of fifty-five patients survived, however, in the group which had persistent auricular fibrillation with myocardial infarction. All those patients with persistent auricular flutter died.

COMMENTS

Deductions derived from a small number of observations must be cautiously interpreted. The errors of statistical evaluation of small groups are illustrated in several instances in this study. For instance, of six patients with auricular flutter with a ventricular rate of 100 or less, only one died (16.6 per cent). Erroneously, therefore, it might be considered a good prognostic omen if auricular flutter with a ventricular rate under 100 complicated myocardial infarction since the mortality of the whole group of 1,247 was 51.5 per cent. This inference is obviously untenable. The deductions in this group that would suggest themselves as probably applicable in general are little more than corroborative of prevalent clinical opinion. Auricular flutter is a known concomitant of serious heart disease in general; it is of similar significance in myocardial infarction. The hazard of the arrhythmia is in general proportional to the rate and duration of the associated tachycardia. This is apparently true in relation to myocardial infarction. The three patients with auricular flutter in Chambers² report all recovered. Sinus rhythm returned in all three and in two without medication. The third patient received digitalis. In one the auriculoventricular block was 4:1 with a slow ventricular rate, and in a second the auricular flutter returned to sinus rhythm the second day; so the rate in one was slow and the duration of the tachycardia in the other was short.

In general there usually is little hazard of embolism if auricular flutter occurs. It

would appear that this is true in myocardial infarction. The treatment of auricular flutter is its elimination, with return to normal rhythm, by the use of digitalis and quinidine. This would seem to hold also in the management of auricular flutter in association with myocardial infarction. Mc-Millan and Bellet¹⁰ stress the urgent need for abolishing flutter in certain cases of severe cardiac failure not associated with myocardial infarction. In certain instances they have given massive doses of digitalis and quinidine in view of the relative risk of the disease and of the drugs. Certainly in the instances of myocardial infarction with tachycardia due to auricular flutter reported in this study quick termination of the arrhythmia was an urgent need. Optimum doses of digitalis and quinidine should have been administered early in practically all instances. Digitalization can be rapidly accomplished by use of oral glycosides if the patient is not vomiting. Otherwise, intravenous lanatoside C may be utilized. Only in patients with a normal ventricular rate without congestive heart failure would medication seem unnecessary under these conditions. In such instances there is relatively little burden imposed upon the heart. The six patients with ventricular rates below 100 all returned to normal rhythm, three of them with no drug treatment and five of the six lived.

Tandowsky¹¹ advocates use of quinidine after the auricular flutter has been converted into auricular fibrillation. He agrees, however,* that in the presence of myocardial infarction it is probably desirable to give both drugs simultaneously. There is the possibility that digitalis, if given alone, may produce ectopic ventricular rhythms which quinidine can prevent.

The experience described has suggested a program for future medication. The appearance of auricular flutter with tachycardia as a complication of myocardial infarction will be considered as requiring emergency treatment; the urgency of the need for termination of the tachycardia

being indicated by the fact that five patients died within twenty-four hours of the onset. Patients with auricular flutter with a normal ventricular rate without congestive failure will receive no medication. Rapid digitalization with a potent glycoside, such as digitoxin, and simultaneous administration of quinidine will be the program. Our practice is to give six tablets of digitoxin (1.2 mg.) at once and quinidine, 6 gr., every two hours until the arrhythmia is abolished. Digitoxin is continued in 0.2 mg. doses daily. In case the patient is unable to take medication orally lanatoside C may be given intravenously, 4 cc. at once, to be repeated in a few hours. Parenteral quinidine prepared according to the formula of Sturnick et al.¹² can be used. This is an effective method and the problem of absorption is eliminated. We intend not to discontinue quinidine because of rash, nausea without vomiting, headache or dizziness; these are of minor importance in relation to the danger of continuance of the auricular flutter.

CONCLUSIONS

1. Auricular flutter occurred in 19 of 1,247 patients with myocardial infarction studied at the Los Angeles County Hospital.
2. When associated with rapid ventricular rate, the arrhythmia constituted a serious hazard resulting in death in all cases in which it did not terminate soon.
3. A program of management is suggested.

REFERENCES

1. MASTER, A. M., DACK, S. and JAFFE, H. L. Disturbances of rate and rhythm in acute coronary artery thrombosis. *Ann. Int. Med.*, 11: 735-761, 1937.
2. CHAMBERS, W. N. Acute myocardial infarction, a study of 100 consecutive cases. *New England J. Med.*, 235: 347-352, 1946.
3. ROSENBAUM, F. F. and LEVINE, S. A. Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction. *Arch. Int. Med.*, 68: 913-944, 1941.
4. JOURDONAIS, L. F. and MOSENTHAL, H. O. Complete auriculoventricular block and auricular flutter with observations of the effect of quinidine sulfate. *Am. Heart J.*, 14: 735-743, 1937.
5. DEMOURA, JOSE PROENCA PINTO. Complete auriculoventricular block and bundle branch block with

* Personal communication.

- intercurrent auricular flutter. *Am. Heart J.*, 32: 794-798, 1946.
6. DIGREGORIO, N. J. and CRAWFORD, J. H. Auricular flutter and complete heart block. *Am. Heart J.*, 17: 114-118, 1939.
7. GRAY, I. and GREENFIELD, I. Auricular flutter with auriculoventricular heart block. *Ann. Int. Med.*, 20: 125, 1944.
8. MILLER, R. and PERELMAN, J. S. Multiple disturbances of rhythm and conduction and unusual auricular T wave in a case of myocardial infarction. *Am. Heart J.*, 31: 501-510, 1946.
9. KATZ, L. N. *Electrocardiography*. 2nd ed., p. 666. Philadelphia, 1946. Lea & Febiger.
10. McMILLAN, T. M. and BELLET, S. Auricular flutter: some of its clinical manifestations and its treatment. *Am. J. M. Sc.*, 184: 33-57, 1932.
11. TANDOWSKY, R. M., OYSTER, J. M., and SILVERGLADE, A. Combined use of lanatoside C and quinidine sulfate in abolition of established auricular flutter. *Am. Heart J.*, 32: 617-633, 1946.
12. STURNICK, M. I., RISEMAN, J. E. F. and SAGALL, E. L. Studies on the action of quinidine in man. *J. A. M. A.*, 121: 917-920, 1943.

The Role of Tonsillectomy in the Management of Recurrent Streptococcal Sore Throat, Rheumatic Fever and Glomerulonephritis*

MAX MICHAEL, JR., M.D.

Atlanta, Georgia

THE concept that foci of infection frequently cause or influence the course of systemic disease, as propounded by Billings and others, has been questioned in recent years. Reimann and Havens pointed out the fallacies in the original reasoning and concluded that careful examination of the evidence failed to reveal good therapeutic results from removal of chronically infected teeth and tonsils for such diseases as rheumatoid arthritis, peptic ulcer, ulcerative colitis and the like.²¹ Cecil, previously one of the chief proponents of the concept, has since concluded that the ideas originally brought forth no longer can be held.⁴ Irons, on the other hand, has recently defended the teachings of Billings and maintains that in cases of iritis and in certain types of infectious arthritis the removal of such foci often benefits the patient.¹⁰

Closely allied in many respects is the question of the role that tonsillectomy should play in the management of patients with recurrent streptococcal sore throats and with the attendant complications of rheumatic fever and glomerulonephritis. Since the tonsils constitute the major site of parasitism by the beta hemolytic streptococcus, it might be expected that removal

of these organs would diminish the chance of infection and of late non-suppurative complications. The present review is concerned with the available evidence on these points.

Many articles concerned with this subject present data in such a way that definite conclusions cannot be drawn. Carefully chosen control groups and adequate follow-up studies are lacking in many of the reports. Moreover, precise bacteriologic and serologic data are frequently absent. An unpredictable source of error is injected when two groups are studied, one having had tonsils removed, and conclusions are drawn as to the subsequent development of streptococcal disease and its complications. This error can be attributed to the fact that in any group of tonsillectomized patients the incidence of previous streptococcal infections is probably higher than in the general population, hence the indication for operation. Such factors were not taken into consideration in many of the conclusions that have been drawn.

For proper evaluation of these problems it is essential to select a group for study and to follow it with careful clinical, bacteriologic and immunologic observations over a period of years. Reviewing case histories

* From the Medical Service, Lawson Veterans Administration Hospital, Chamblee, Georgia, and the Department of Medicine, Emory University School of Medicine, Atlanta, Ga., Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

without personal observation of the patients concerned is productive of many errors. This review strives to attain a more critical perspective with regard to frequently accepted axioms concerning the management of streptococcal disease and its late complications, and to point out the need for more complete data.

STREPTOCOCCAL SORE THROAT

Removal of the tonsils will obviously decrease the incidence of tonsillitis. However, while this procedure removes from the throat the largest single body of tissue capable of harboring the streptococcus and other organisms, it leaves behind large areas of lymphoid tissue easily capable of becoming infected. The effect of tonsillectomy on the subsequent development of sore throats may be evaluated in two ways: first, by recording the incidence of sore throats over a period of years in tonsillectomized and in non-tonsillectomized persons; second, by observing the incidence of sore throats during a single outbreak of streptococcal disease.

It must be emphasized in this discussion of the role of tonsillectomy in patients with sore throats that bacteriologic and serologic studies have seldom been reported. This becomes more significant in the light of recent studies which have shown that in a large percentage of patients with acute sore throat during non-epidemic times the streptococcus cannot be incriminated as the etiologic agent.⁵

Paton observed a group of 909 girls attending a boarding school in England between the years of 1930 and 1939.¹⁶ Histories were taken of previous health and records were kept of illnesses while in the school. Fifty-seven per cent of the girls had had tonsillectomy prior to admission. Of interest is the fact that remnants of tonsillar tissue were present in 40 per cent of this group. This, however, represents the results to be expected in the usual tonsillectomy. The incidence of "follicular or lacunar tonsillitis" was about five times as great among those in whom no operation had

been performed as in the tonsillectomized group.

The following figures, taken from Paton and calculated on admission rate per 100 girls, were broken down further as to whether or not adenoids as well as tonsils had been removed.

	Operation			No Opera- tion
	Tonsils and Ade- noids	Tonsils Only	Ade- noids Only	
No. of girls	435	57	24	393
Pharyngitis (%)	40	53	54	41
Tonsillitis (%)	1	2	4	5

"The reduction in tonsillitis after tonsillectomy . . . was not, that is to say, accompanied by a corresponding increase in sore throat from other causes; it was a true reduction." Paton stresses that too much reliance must not be placed on percentages calculated from such small numbers. The important feature was, however, that the incidence of pharyngitis in the two groups was the same. Cultural studies were not reported in this survey.

Kaiser's study of 4,400 children in Rochester, New York, has provided many interesting data.¹³ At least two febrile attacks of tonsillitis occurred during the first seven years of life in approximately 38 per cent of the 4,400 children. Tonsillectomy for one indication or another was advised for the entire group but for various reasons was performed in only 2,200. The incidence of previous sore throats was not significantly different in the two groups. At intervals of one, three and ten years after operation had been advised, the patients were re-examined and their parents were interviewed as to illnesses of the children in the intervening years. This study is open to criticism on several grounds. Parents whose children have had tonsillectomy are likely to emphasize their good health after operation. Furthermore, anamnestic histories are necessarily fraught with error. Never-

theless it is interesting to compare the figures for the two groups. In the first three-year period following operation sore throats occurred in 36 per cent of the non-operated group as compared with 3 per cent of the operated group.

At the ten-year follow-up 10 per cent of the operated group had had sore throats as compared with 35 per cent of the non-operated group. Kaiser correctly emphasizes that even in the absence of tonsils, sore throats involving the pillars and pharynx may still occur and cause illness as severe and as detrimental to the health of the child as that caused by acute tonsillitis. Nevertheless, his study provides evidence that in patients subject to repeated severe sore throats, tonsillectomy may diminish the likelihood of further attacks of sore throat.

Studies of population groups living under similar conditions and having comparable exposure to throat infections have brought out many interesting points. The Commission on Acute Respiratory Diseases reported detailed observations on an outbreak of type 5 beta hemolytic streptococcus tonsillitis and pharyngitis presumably caused by eating infected eggs.⁶ In the group studied tonsils were present in fifty-eight, tonsillar remnants (tags) in twenty-three and complete absence of tonsillar tissue in six. No mention is made, however, of the incidence of tonsils in the exposed but non-infected group. In patients whose tonsils were absent the disease was not modified to an important degree as compared with those whose tonsils were present. However, in the group with tonsils a predominant growth of streptococci was found more frequently than in the tonsillectomized group. Also, exudate was more abundant in patients with tonsils. Furthermore, at the end of six weeks 50 per cent of the individuals with tonsils still had positive throat cultures whereas only 20 per cent of the tonsillectomized persons had positive cultures. The difference is statistically significant.

Rantz, Spink and Boisvert have made a careful study of a food-borne throat infection in a military hospital group. The

causative organism was type 1 beta hemolytic streptococcus.¹⁸ Fifty-eight patients, all equally exposed to the offending food, were selected for further investigation. Sixty per cent of these became infected, as judged by cultural and serologic studies. It was not possible to determine all factors preventing infection in the other 40 per cent but a striking factor was the presence of tonsils in 48 per cent of the non-infected as compared to 94.3 per cent of the infected group. They contrasted this observation with those made in another large group of cases in which infection by a variety of types of hemolytic streptococci occurred. In this study the absence of tonsils did not interfere with the development of streptococcal sore throat. Tonsillectomy had been performed in 33 per cent of the group suffering from streptococcal infections and in 34.4 per cent of the group with non-streptococcal throat infections.¹⁹

Bloomfield studied a group of nurses during the course of a year.² In this period of time streptococcal tonsillitis occurred in 8 per cent of those tonsillectomized and in 30 per cent of those not having had a tonsillectomy. He concluded that in the group under study the absence of tonsils did offer considerable protection against infection with the hemolytic streptococcus.

A large group of patients diagnosed as having endemic pharyngitis was observed by the Acute Respiratory Disease Commission.^{5*} These patients primarily were recent inductees in a large Army training center. In those patients with exudative pharyngitis the frequency of positive culture for hemolytic streptococci and the antibody response was the same irrespective of the

* In passing it should be pointed out that these workers have demonstrated that in the patients with exudative pharyngitis, in non-epidemic times, beta hemolytic streptococci are isolated (in predominant numbers) in 50 per cent of the patients, and that in only 50 per cent of those with beta hemolytic streptococci is an antibody rise indicative of streptococcal infection demonstrated. De Wesselow had arrived at similar conclusions in England in 1935 when he noted a heavy predominance of beta hemolytic streptococci in only 25 per cent of 354 patients with tonsillitis seen in the clinic over a period of one year.⁷

presence or absence of tonsillar tissue. Rantz, Spink and Boisvert, as mentioned previously, have pointed out that tonsillar tissue seems to play no appreciable role in the development of throat infection with the hemolytic streptococcus except in explosive outbreaks due to one specific type.¹⁸

Although the evidence is not complete and is at times conflicting, the data at hand would seem to suggest the following. The frequency of sore throats appears to be reduced in those individuals whose tonsils have been removed. In outbreaks of streptococcal disease caused by a single type of the organism, tonsillectomized individuals similarly appear to be protected to some extent. When infection is caused by more than one type of the streptococcus, tonsillectomized individuals apparently are not spared to any significant degree. It must be emphasized, however, that most reports have not included bacteriologic studies. This becomes even more important when it is realized that endemic pharyngitis in a large percentage of cases is not caused by the hemolytic streptococcus.

Most authorities advise tonsillectomy in patients subjected to repeated severe sore throats, by which is meant one or more attacks a year. It is to be re-emphasized, however, that this does not insure against reinfection of the pharynx by the hemolytic streptococcus or by other pathogens.

RHEUMATIC FEVER

The concept that rheumatic fever represents an abnormal response to a streptococcal infection, particularly of the pharynx, has been accepted by most writers.²⁵ Many workers have shown that a rise in anti-streptolysin titer, signifying infection by the beta hemolytic streptococcus, occurs in nearly all patients with acute rheumatic fever. Rantz, Boisvert and Spink in recent war experience with group A beta hemolytic streptococcal disease have re-emphasized the rôle of this organism in the pathogenesis of rheumatic fever.¹⁷

Granted that acute rheumatic fever is

preceded by infection with the streptococcus in most, if not all, instances, it is natural to inquire whether removal of a large focus favorable for growth of the organism, namely, the tonsils, will prevent the development or alter the subsequent course of the disease. In an attempt to answer such questions one is forced to rely on statistical reports of large groups, despite the fact that there are many sources of error in the collection of such data.

Kaiser's previously mentioned study is of interest.¹³ Before tonsillectomy the incidence of chorea, rheumatic fever, muscular pains and rheumatic carditis was the same in both groups. The two groups were of comparable ages. After operation the figures were as follows: Chorea: operated group, 1.1 per cent, control, 0.6 per cent; rheumatic fever: operated, 2.3 per cent, control, 3.5 per cent; muscular pains: operated, 7.8 per cent, control, 9 per cent; rheumatic carditis: operated, 1.1 per cent, control, 1.3 per cent. None of these differences appears to be significant.

In another study Kaiser analyzed the records of 48,000 children, histories having been obtained from the parents.¹² Twenty-eight thousand of this group had had tonsillectomy, and among these there were 339 cases of rheumatic fever (1.9 per cent) as compared to 876 cases (3.0 per cent) in the unoperated group. Growing pains, chorea and rheumatic carditis were of similar incidence. He points out that children without tonsils do not escape rheumatic fever in sufficient numbers to justify the procedure of universal tonsillectomy as a preventive measure.

Similar observations have been recorded by other investigators. Wallace and Smith studied the records of children in Edinburgh.²⁶ They divided their patients into two groups: Group I comprised 403 children whose tonsils had been removed before the age of five and who had not had rheumatic fever. Group II comprised 574 children whose tonsils were removed in later childhood. Before "school leaving age" acute rheumatism, i.e., chorea, rheumatic fever

and carditis, had occurred in 7.2 per cent of the first group as compared with 4.2 per cent of the second group. There was a higher percentage of males in the first group which, they believe, should if anything make the incidence of rheumatic fever lower. They concluded that the procedure fails completely to protect a child against rheumatic fever and that it may even render him more liable to develop the disease. It should be pointed out, however, that in a group of children under five whose tonsils are removed there is apt to have been more preceding streptococcal disease. The study of Campbell and Warner is similar.³ Of 124 children with "complete removal of tonsils" 15.3 per cent subsequently developed rheumatic fever. There were 843 who never had tonsillectomy and 18.6 per cent of these developed rheumatic fever.

It would appear from the above recorded surveys that the operation of tonsillectomy will not offer protection against the development of rheumatic fever, hence the procedure should not be offered as a universal prophylactic. This seems logical for although tonsillectomy will remove a large body of tissue that is capable of harboring streptococci, nevertheless considerable amounts of lymphoid tissue are left in the nasopharynx even after the cleanest of tonsillar and adenoid enucleations. Moreover, rheumatic fever may be precipitated by a transient and superficial infection of the pharynx by the streptococcus.

Effect of Tonsillectomy on Recurrences. Hunt and Osman⁸ were among the first to question the efficacy of tonsillectomy in the management of the patient with rheumatic fever. They conducted follow-up studies on 144 rheumatic fever patients, of whom sixty-six had had tonsillectomy and seventy-eight had not. Recurrences were noted in 53 per cent of the operated group as compared with 42 per cent in the control group. Further analysis of these data in relation to recurrences after a first and second attack revealed a similar situation. These workers concluded that tonsillectomy was not a

certain protection against recurrences, and that, if anything, it was inductive of a higher recurrence rate. Kaiser makes the unqualified statement that recurrent attacks of rheumatic fever are as likely to occur in children whose tonsils have been removed as in those in whom they are still present.¹³ In his group of 439 children observed for five years those who had developed the first attack of rheumatic fever before tonsillectomy had a recurrence rate of 28 per cent as compared with 27 per cent for the group whose first attack developed after tonsillectomy. This opinion is also held by Stokes,²⁴ Janeway¹¹ and Rantz.²⁰ Spink has the impression that the removal of tonsils does decrease the incidence of subsequent attacks of rheumatic fever although he states that for this view he has no statistical data.²³ If a patient with a history of rheumatic fever has repeated attacks of acute tonsillitis, he should have a tonsillectomy during an inactive phase of his disease in the hope of decreasing the incidence of sore throats. The chances are that it will not lessen the likelihood of recurrence of rheumatic fever.

Tonsillectomy in Relation to the Late Effects of Rheumatic Fever. The proper evaluation of this aspect of the problem is made difficult because of the extreme variability in the clinical course of rheumatic fever. Carditis with its subsequent valvular and myocardial scarring is the most serious of the sequelae of rheumatic fever. If it could be shown that tonsillectomy diminishes the incidence of carditis, the procedure would be not only advisable but imperative in the management of rheumatic fever. Such, however, does not appear to be the case.

The outcome of a group of 597 children who developed their first attack of rheumatic fever between the ages of five and ten years and who were followed for a period of ten years is presented by Kaiser.¹³ These patients were divided into three groups: (1) those whose tonsils remained in during the entire period of observation; (2) those whose tonsils were removed after the first attack; and (3) those whose tonsils were

removed prior to the first attack. The outcome of these groups is as follows:

<i>Group</i>	<i>No.</i>	<i>Died, Per Cent</i>	<i>Recurred, Per Cent</i>
1	156	13	46
2	254	4	44
3	187	7	48

The incidence of carditis was the same in the groups, but it was the author's impression that fatal carditis was less frequently noted in the tonsillectomized group. The figures of Allen and Baylor¹ tend to corroborate this.

Among other studies of interest is that of Campbell and Warner³ who noted that the incidence of carditis was not influenced by the presence of tonsils.

It would appear that tonsillectomy should be performed in patients with rheumatic fever for the same reason as in non-rheumatic subjects, namely, in an attempt to prevent frequent attacks of tonsillitis. It is the general belief, however, that the procedure should not be performed during the active stage of the disease. No sound evidence is available which would indicate that the procedure will lessen the patient's chance of recurrence or that it will appreciably alter the late effects of the disease.

GLOMERULONEPHRITIS

Most authors agree that acute glomerulonephritis is preceded most frequently by infection with group A beta hemolytic streptococcus.¹⁵ In the majority of instances the primary streptococcal infection is in the nasopharynx. Unlike acute rheumatic fever, however, nephritis may also follow streptococcal skin infections. Recurrences of glomerulonephritis are similarly preceded by streptococcal pharyngeal infections in most instances. The problem of the role of tonsillectomy in the management of glomerulonephritis is essentially the same as that in rheumatic fever, i.e., does the operation prevent the disease, modify its course or prevent recurrences.

Turning again to the work of Kaiser,¹² one finds the statement that the absence of tonsils gives the child only a slightly better chance of escaping glomerulonephritis. Illingworth observed 365 patients with glomerulonephritis at the Great Ormond Street Hospital for sick children.⁹ Three hundred one of these patients were in the acute stage. Twenty per cent of the children had had tonsillectomy before admission in their acute episode as compared with an overall incidence for tonsillectomy of 9 per cent in the general population of comparable age groups. He believed that the procedure not only did not prevent the disease but that in several instances it actually precipitated an episode of acute glomerulonephritis. The factual evidence for the latter statement is, however, rather meager.

In considering the effect of tonsillectomy on the course of glomerulonephritis one finds the same paucity of facts on the ultimate outcome of the disease as were found in the study of rheumatic fever. One of the most comprehensive studies of acute glomerulonephritis is that recently reported from Sweden by Rudebeck.²² He has followed 318 patients with acute and subacute glomerulonephritis over a period of twenty-three years. In this group 69 per cent were listed as recovered, 19 per cent as uncertain and 11 per cent as not recovered. In the period from 1923 to 1933 tonsillectomies were done early in the disease. This apparently had no effect on the ultimate outcome of the disease, for of the fifty-two tonsillectomized patients 67.3 per cent recovered, in 21.2 per cent the outcome was uncertain and 11.5 per cent did not recover. Of sixty-three patients not operated upon 69.8 per cent recovered, the outcome was uncertain in 19.0 per cent and 11.1 per cent did not recover. Similarly he was unable to detect any differences in the recurrence rate in the tonsillectomized and non-tonsillectomized group. Rudebeck concludes that those reports of apparent improvement in the course of the disease are not valid either because the controls were not adequate, because follow-up

studies were insufficient or because data were misinterpreted.

appear to be those for tonsillectomy in general, namely, for frequent episodes of acute tonsillitis.

Illingworth's⁹ analysis of the outcome of the 301 patients with acute glomerulonephritis is shown in Table 1. He concludes that in no instance can it be said that tonsillectomy had any immediate beneficial

COMMENT

It is not the purpose of this review to attempt to draw sweeping conclusions but

TABLE 1*
EFFECTS OF TONSILLECTOMY ON THE OUTCOME OF PATIENTS WITH GLOMERULONEPHRITIS

	Cases	Urine on Discharge			Died in Acute Stage	Subsequent History		Latent or Active	Re-examination 1 to 12 Years after Onset	
		Un-known	Ab-normal	Normal		Died	Exacer-bation		Doubt-ful	Healed
Tonsillectomy more than 6 months before onset of nephritis.....	61	28	28	5	0	2	0	15	3	3
Operation probably caused nephritis.....	15	7	8	0	0	0	0	4	0	0
Tonsillectomy performed as therapeutic measure within 6 months of onset.....	119	67	44	8	1	2	7	23	4	7
Control children in whom tonsillectomy was not performed.....	106	45	52	8	13†	0	4	20	4	3
Totals.....	301	147	132	21	14	4	11	62	11	13

* From Illingworth.⁹
† Most died in first few days of disease.

effect on the nephritis, nor that it had any effect on the subsequent course of the disease.

It would appear that tonsillectomy offers little in the management of the patient with glomerulonephritis. Certainly it will not prevent the disease and apparently it does not alter its course. There is fairly general agreement that tonsillectomy during the acute stage of glomerulonephritis is quite apt to provoke an exacerbation with an increase in the elements in the urinary sediment, a rising NPN and further elevation of blood pressure.¹⁴ In the quiescent or latent stage of glomerulonephritis the removal of tonsils in the hope of preventing recurrence of the disease or the likelihood of further renal damage lacks supportive evidence. In patients with glomerulonephritis the indications for tonsillectomy would

rather to present evidence on the question of the efficacy of tonsillectomy in the disease states discussed. The need for more carefully controlled studies with adequate bacteriologic and serologic data cannot be over-emphasized. Tonsillectomy is frequently recommended with claims that dramatic changes in health may ensue. No attempt has been made to go into the effect of the procedure on the growth, development and general health of the child. Tonsillectomy is not completely without risk. Rare though complications may be, they do include fatal hemorrhage and pulmonary abscess. Furthermore, evidence seems to indicate that the operation increases the likelihood of developing bulbar poliomyelitis during an epidemic period. Weighing all factors, it would seem that tonsillectomy, not a completely innocuous procedure, should not be

performed indiscriminately. Each individual case must be considered on its own merits.

CONCLUSIONS

Patients with repeated episodes of acute severe sore throats can be expected to have a decreased number of attacks after tonsillectomy. The available evidence does not indicate that tonsillectomy will prevent or will appreciably alter the course of acute rheumatic fever or of acute glomerulonephritis, or that it will diminish the incidence of recurrence of these diseases.

Further careful clinical, bacteriologic and immunologic studies on a large unselected group of people are needed before positive conclusions can be drawn.

REFERENCES

1. ALLEN, W. B. and BAYLOR, J. W. The influence of tonsillectomy upon the course of rheumatic fever and rheumatic heart disease. *Bull. Johns Hopkins Hosp.*, 63: 111, 1936.
2. BLOOMFIELD, A. L. Bacteriologic observations in acute tonsillitis with reference to epidemiology and susceptibility. *Arch. Int. Med.*, 32: 483, 1923.
3. CAMPBELL, M. and WARNER, E. C. A study of rheumatic disease in children. *Lancet*, 1: 61, 1930.
4. CECIL, R. Rise and Fall of Focal Infection. Interstate Postgraduate Assembly of North America, p. 301, 1941.
5. Commission on Acute Respiratory Diseases. Endemic exudative pharyngitis and tonsillitis. *J. A. M. A.*, 125: 1163, 1944.
6. Commission on Acute Respiratory Diseases. A study of a food-borne epidemic of tonsillitis and pharyngitis due to β hemolytic streptococcus, type 5. *Bull. Johns Hopkins Hosp.*, 77: 143, 1945.
7. DE WESSELOW, O. L. V. S., GOADBY, H. K. and DERRY, D. C. L. Tonsillitis and albuminuria. *Brit. M. J.*, 1: 1065, 1935.
8. HUNT, G. H. and OSMAN, A. A. The results of tonsil-

- lectomy in acute rheumatism in children. *Guys Hosp. Rep.*, 73: 383, 1923.
9. ILLINGWORTH, R. S. Tonsillitis and nephritis of childhood. *Lancet*, 2: 1013, 1936.
10. IRONS, E. E. The theory of focal infection: its influence on the practice of medicine. *Proc. Inst. Med. Chicago.*, 16: 265, 1946.
11. JANEWAY, C. A. Personal communication.
12. KAISER, A. D. Children's Tonsils In or Out. A Critical Study of the End Results of Tonsillectomy. Philadelphia, 1932. J. B. Lippincott Co.
13. KAISER, A. D. Significance of the tonsils in the development of the child. *J. A. M. A.*, 115: 1151, 1940.
14. LOEB, R. F. A Textbook of Medicine. Edited by R. L. Cecil. 7th ed. Philadelphia, 1947. W. B. Saunders.
15. LONGCOPE, W. T. Some observations on the course and outcome of hemorrhagic nephritis. *Tr. Am. Clin. & Climatological Ass.*, p. 1, 1939.
16. PATON, J. H. P. The tonsil-adenoid operation in relation to the health of a group of school girls. *Quart. J. Med.*, 12: 119, 1943.
17. RANTZ, L. A., SPINK, W. W. and BOISVERT, P. J. The etiology and pathogenesis of rheumatic fever. *Arch. Int. Med.*, 76: 131, 1945.
18. RANTZ, L. A., SPINK, W. W. and BOISVERT, P. J. Hemolytic streptococcus sore throat. Detailed study of the simultaneous infection of a large number of men by a single type. *Arch. Int. Med.*, 76: 278, 1945.
19. RANTZ, L. A., BOISVERT, P. J. and SPINK, W. W. Hemolytic streptococcal and non-streptococcal diseases of the respiratory tract. *Arch. Int. Med.*, 78: 369, 1946.
20. RANTZ, L. A. Personal communication.
21. REIMANN, H. A. and HAVENS, W. P. Focal infection: a critical review. *J. A. M. A.*, 114: 1, 1940.
22. RUDEBECK, JOHAN. Clinical and prognostic aspects of acute glomerulonephritis. *Acta med. Scandinav.*, Supplement 173, 1946.
23. SPINK, W. W. Personal communication.
24. STOKES, JR., J. Personal communication.
25. SWIFT, H. F. The relationship of streptococcal infections to rheumatic fever. *Am. J. Med.*, 2: 168, 1947.
26. WALLACE, H. L. and SMITH, A. B. The effect of early tonsillectomy on the incidence of acute rheumatism. *Edinburgh M. J.*, 43: 452, 1936.

Seminars on Congestive Failure

Pathogenesis of Renal Dysfunction during Congestive Heart Failure*

STANLEY E. BRADLEY, M.D. and WILLIAM D. BLAKE, M.D.†

New York, New York

CONGESTIVE heart failure involves a complex of disorders affecting nearly every organ system of the body. No one denies that the cardiac lesion is of primary importance in initiating the chain of events that culminates in a rising venous pressure, accumulation of edema and evidences of renal dysfunction. There is sharp disagreement regarding the sequential position and the relative importance of these changes in connection with the cardiac disturbance. One important cause for dispute lies in the emphasis placed upon the role of the kidney in the formation of edema. On the one hand, an elevation of venous and capillary blood pressures is regarded as instrumental in diverting fluid from the vascular bed into the tissues and thus in provoking an overactive conservation of water and salt by the kidneys.^{1,2} On the other hand, abnormal renal retention of water and salt due to the "cardio-circulatory" imbalance is believed to result in an expansion of plasma volume and an increase in venous pressure with the coincidental development of edema.^{3,4} This paper is devoted to an analysis of renal abnormalities in congestive failure with the purpose of reconciling these opposing views.

EVIDENCE OF RENAL DYSFUNCTION DURING FAILURE

There is little anatomic evidence of renal damage in congestive heart failure.

The kidneys may be enlarged as a result of venous engorgement and dilatation of the peritubular capillaries.¹ The glomerular capillaries are rarely if ever involved. Occasionally cloudy swelling and fatty infiltration of tubular cells are found but as a rule the parenchyma is unaffected. In contrast, marked changes in the character of the urine occur. Proteinuria and cylindruria develop in the majority of patients and microscopic hematuria is occasionally encountered.^{5,6} The urea clearance and phenolsulfonphthalein excretion are usually depressed. It is particularly interesting that the urinary specific gravity tends to rise and to remain fixed at an unusually high level in many cases. This fact has been cited¹ as evidence of a fundamentally adequate renal function, other changes being incidental to the augmented activity of the kidney in conserving water and electrolytes. Perhaps the most striking and certainly the most important renal dysfunction is retention of water and sodium.

It has been recognized^{7,8} for many years that restriction of water and salt intake may control and even prevent edema. This phenomenon has been placed upon a quantitative basis only recently.^{9,10} The sodium ion appears to be selectively affected in failure since water loading alone is not uniformly followed by a gain in weight whereas increased sodium intake in association with adequate hydration results in

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York, N. Y. Aided by a grant from the Edward N. Gibbs Prize Fund of the New York Academy of Medicine.

† Post-graduate Fellow of the United States Public Health Service.

striking edema formation. Other electrolytes are relatively undisturbed so that retention of sodium need not involve a linked retention of chloride. Although chloride does tend to follow sodium, the urinary sodium/chloride output ratio usually falls.¹¹ The kidneys fail to regulate the total body content of sodium and water normally but they usually continue to maintain the plasma composition within normal limits.¹² Occasionally marked azotemia with retention of all the components of the non-protein nitrogen is encountered and, rarely, the serum concentration of sodium and chloride may fall, apparently because of sodium restriction and failure to eliminate excess body water.²

RENAL HEMODYNAMIC ADJUSTMENTS DURING FAILURE

Recent investigations¹³⁻¹⁶ have sought to define the renal hemodynamic adjustments during congestive failure in relation to sodium and water excretion. A variable depression of renal blood flow and glomerular filtration rate has been found. In some individuals these values may be reduced to as low as one-third and one-half the normal values, respectively, when edema is present. There is a definite tendency to return toward the normal with compensation. Blood flow is always affected to a more marked degree than filtration and the percentage of plasma filtered at the glomerulus consequently increases. Since the change in blood flow occurs in the absence of a similar change in arterial pressure and since it is apparently independent of the level of renal venous pressure, decompensation must evoke a striking increase in renal vascular resistance. Most observers believe that both afferent and efferent arterioles are involved, because the glomerular filtration rate tends to fall and the filtration fraction rises. In this view, diminished filtration is a manifestation of diffuse intrarenal vasomotor activity which presumably affects each glomerulus to some extent. These data do not preclude the possibility that filtration is reduced because a certain proportion of

nephrons become completely inactive. In such a case the vasomotor activity might involve afferent arterioles almost exclusively or blood might perfuse non-functioning glomeruli, the behavior of the filtration fraction then having little meaning in terms of glomerular dynamics. Whatever its distribution, intrarenal vasoconstriction is characteristic of heart failure and it accounts in part if not entirely for the diminution of glomerular filtration.

The kidneys appear to operate in the systemic circulation as vascular buffers. Intrarenal vasoconstriction results in the diversion of a considerable quantity of blood to other tissues and thus serves to support arterial pressure and to supplement, in effect, the cardiac output.¹⁷ This response has been observed under many circumstances, e.g., in hypotensive states following blood loss, trauma and fever; on assumption of the upright position; during chronic anemia, in Addison's disease, exercise, fright and in anger; as well as following the injection of various pressor agents. These renal vascular responses differ mainly in the degree to which afferent arteriolar constriction occurs. Many conditions characterized by a reduction in *circulating* blood volume (shock, orthostasis, Addison's disease, chronic anemia) present evidence of preponderant afferent arteriolar constriction.¹⁸ This activity may so interfere with the nutrition of the kidney in shock that irreversible damage may ensue.¹⁹ It is true that abundant and apparently reliable evidence indicates a marked expansion of blood volume in congestive failure.²⁰ But a considerable portion of this volume is probably pooled in dilated veins of the dependent extremities, the abdomen and the abdominal viscera so that effective *circulating* blood volume is reduced. Measurements of this variable are not feasible at present and this possibility cannot be explored. In any event, the patient with failure behaves as if inadequate venous return and/or cardiac inefficiency interferes with normal circulatory regulation.

A reduction of cardiac output is demonstrable

in most patients with congestive failure at rest.^{21,22} A compensatory increment in total peripheral resistance is necessary to maintain arterial pressure within normal limits in these individuals and renal vasoconstriction out of proportion to that elsewhere in the body is not unexpected since this is a situation dynamically similar to shock. Myers²³ has found that excessive compensatory vasoconstriction also develops in the hepatoportal circuit, which is not surprising in view of the increasing evidence that this vascular bed is also important in circulatory adjustments. Excessive compensatory vasoconstriction in some individuals may elevate the arterial pressure well above normal values. In a small group of patients decompensation occurs in association with an augmented cardiac output,^{22,24-26} the so-called "high output failure" of cor pulmonale, arteriovenous fistula, thyrotoxicosis, Paget's disease, beriberi and chronic anemia. Obviously peripheral vascular resistance is much diminished in these cases but intrarenal vasoconstriction develops nonetheless.¹⁴ It may be surmised that this is a response to an instability of arterial pressure resulting from an inefficient maintenance of cardiac output. This assumption finds support in the fact that cardiac output tends to *fall* and pulmonary arterial pressure tends to rise during exercise in both types of failure, indicating outright or potential cardiocirculatory imbalance exaggerated or unmasked by stress. The disturbance in renal blood flow is also grossly exaggerated during exercise.^{29,30}

Little is known regarding the *mediation of vasoconstriction* in the kidney or in other parts of the body during failure. Starling³¹ suggested that a preliminary fall in arterial pressure might elicit such a response to return blood pressure to normal and thereby to assure continued perfusion of the brain. This view has much to recommend it since hypotension develops frequently and since the inadequate response of cardiac output during stress predisposes to a fall in arterial pressure. This stimulus might be expected to influence renal function by reflex action,

but recent work by Mokotoff and Ross³² suggests that renal vasoconstriction in failure does not require continuous activity of the autonomic nervous system. In their studies spinal anesthesia did not alter renal blood flow provided arterial pressure was maintained by ephedrine. However, ephedrine has been found to cause intrarenal vasoconstriction³³ and it is possible that the effect of spinal anesthesia may have been masked. Moreover, high spinal anesthesia does not alter the blood flow through the normal kidney during rest in recumbency³⁴ although it does alter profoundly the ability of the vascular system as a whole to adjust to changes of state. Elevation of the body after intrathecal administration of procaine is quickly followed by hypotension and syncope. Possibly autonomic reflexes are instrumental in establishing a given state of vascular tonus and in maintaining or altering it during stress as needs demand; whereas independent local mechanisms maintain the imposed tonic state during periods of little change. According to this point of view therefore the constancy of renal blood flow during spinal anesthesia does not exclude autonomic activity as an initiating cause of vasoconstriction during failure since the autonomic system is called upon to act only during stress. The role of hypothetical humoral agents in mediation of the vasoconstrictive response is difficult to evaluate. It has long been believed that hypertension during failure may arise from interference with renal blood flow and stimulation of renin formation. Merrill³⁵ has provided evidence for this view by finding an increased renin content of the renal venous blood in eight of eleven patients with chronic congestive failure who had no intrinsic renal disease. He does not state whether the blood pressure was elevated in these patients. Renin cannot be considered a cause of renal vasoconstriction since renal ischemia presumably must precede its production. No other humoral agents have been detected in congestive failure although it is not unlikely that certain internal secre-

tions may be active in promoting retention of salt and water.

There is little doubt that marked *renal anoxia* may develop in certain patients with congestive failure but it appears to be a late manifestation occurring long after edema formation has begun, having little significance in the development of the clinical syndrome of failure. Renal anoxia similar to that obtaining early in failure appears to enhance salt and water excretion. A marked polyuria develops soon after reduction in oxygen saturation of the blood by inhalation of oxygen-poor gas mixtures³⁶ and sodium, potassium and chloride excretion rises.³⁷ It seems quite unlikely therefore that the anoxia-producing effect of renal ischemia is implicated. The change in renal blood flow is probably significant in relation to sodium and water retention only insofar as it is associated with a depression in glomerular filtration.

GLOMERULAR FILTRATION AND TUBULAR REABSORPTION OF SODIUM AND WATER DURING FAILURE

Glomerular filtration is of crucial importance in this connection because it has been shown¹⁷ that water and the sodium and chloride ions are excreted by filtration alone. A very large volume of filtrate—in excess of 180 L.—is formed daily whereas only a small quantity of urine is eliminated, indicating tubular reabsorption of almost all the filtrate. Since such a small proportion of the filtrate is excreted, it has been customary to think of tubular activity as decisive in determining output. Water reabsorption occurs largely in the proximal segment where it apparently follows sodium reabsorption passively with maintenance of “iso-osmoticity” of urine in the proximal segment.^{38,39,40} Numerous studies^{41,42} have demonstrated that distal tubular water reabsorption is an active process, independent of sodium reabsorption, which is carried out under the influence of the neurohypophysis. This apparatus is said to be activated by “osmoreceptors” located in the region supplied by the external carotid.⁴³ The

osmoreceptors respond to changes in plasma osmotic pressure, especially when due to changes in the concentration of plasma sodium. Sodium excretion, on the other hand, may be controlled by minute fluctuations in filtration.⁴⁰ The usual range of excretion (20 to 160 mEq./day) under normal circumstances represents only from 0.01 to 0.1 per cent of the total filtered sodium. It has been postulated^{40,44} that a constant absolute quantity or proportion of most of the filtered sodium is reabsorbed in the proximal segment and that a limited transfer mechanism in the distal segment controls output in association with changes in filtration; increased filtration serving to increase slightly the distal tubular loading of sodium beyond the capacity of the transfer mechanism so that increased excretion occurs, whereas decreased filtration reduces the load below the transfer capacity and permits reabsorption of almost all filtered sodium. Unfortunately, the changes in filtration necessary to such a mechanism are too small to be detected by methods at present available and the hypothesis cannot be tested critically.

In conformity with this view, Mokotoff, Ross and Leiter¹⁵ have found that the proportion of sodium reabsorbed remains unchanged within narrow limits in both normal and decompensated patients. Since filtration is usually somewhat reduced and *total* sodium reabsorption depressed, they conclude that sodium retention in heart failure is a result of the decreased filtration rather than increased tubular reabsorption of sodium. The quantities involved in these calculations differ so greatly in magnitude that the mathematic manipulations and correlations may be very misleading. The quantity of sodium excreted per minute under all circumstances is negligibly small and in consequence an excellent correlation between filtered load and sodium reabsorption is inevitable over a wide range. In the published data,¹⁵ however, a departure from the predicted relation is evident at high plasma levels of sodium even though filtration has increased, de-

noting the intervention of a change in tubular reabsorption as a factor of importance. In evaluating the reduction in *total* sodium reabsorption it must be remembered that such a reduction does not preclude increased reabsorptive activity by a smaller

published work by Earle⁴⁵ and Leiter⁴⁶ has disclosed a significant fall in the transfer maxima of sodium *p*-aminohippurate (PAH Tm). It seems likely therefore that the glomerulotubular imbalance is not as great as it appears to be in many patients and that reabsorption may be relatively increased.

Certain additional considerations are opposed to the view that deficient filtration alone accounts for sodium retention. In Figure 1 data from the literature¹³⁻¹⁶ for filtration rate during and after recovery from congestive failure are plotted. Filtration rate fell within normal limits (lower limit about 90 cc. per min.⁴⁷) in a significant proportion. Unquestionably, the values were low normal or abnormally low in the majority but this change appears to have had no clear-cut relationship to the degree of water and salt retention evident as edema in these individuals. Of even greater importance is the observation that filtration showed no consistent change during return to compensation. Very small increments may have served in some instances to promote diuresis and mobilization of edema but in at least seven patients filtration fell during compensation without in any way preventing the diuretic response to therapy. Salt and water diuresis has also been observed acutely following intravenous injection of digoxin in decompensated patients before any change took place in glomerular filtration or renal blood flow.⁴⁵ Finally, filtration may be much more markedly disturbed than it is in most recorded instances of heart failure without evidence of edema formation. This is particularly true when filtration is disturbed by intrinsic renal disease such as nephrosclerosis, without a corresponding alteration in tubular function.⁴⁸ These patients often display a remarkable ability to regulate sodium and water balance and they may live for years with filtration rates as low as any of those recorded in congestive failure, responding to excesses or deficits of salt and water with normally appropriate although often less exact and speedy adjustments. In chronic

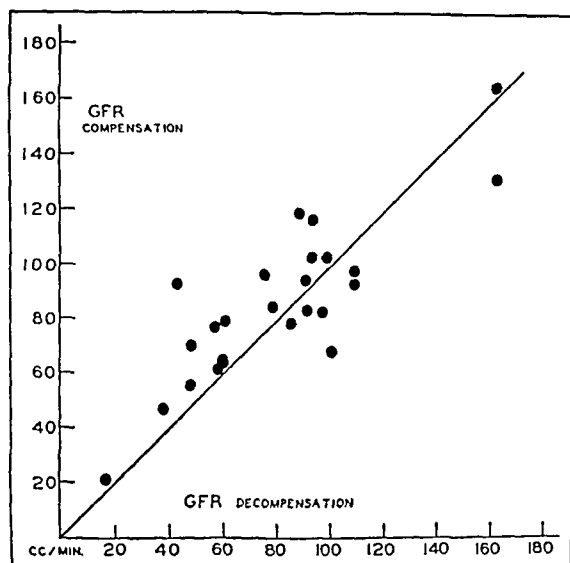


FIG. 1. Change in glomerular filtration rate during recovery from congestive heart failure. Values for glomerular filtration rate (GFR) taken from Seymour et al.,¹³ Merrill,¹⁴ Mokotoff, Ross and Leiter¹⁵ and Briggs et al.¹⁶ during decompensation are plotted against values obtained in the same individuals after recovery. The points above the diagonal are from patients in whom filtration rose during compensation whereas those below the line denote a fall in filtration. Filtration was usually reduced in failure close to or below the lower limit of normal (about 90 cc. per minute). In many patients there was no significant change in filtration with recovery and in a few it fell.

number of functioning nephrons. Filtration may be diminished as a result of diffuse or focal glomerular involvement. Most writers have made the tacit assumption that the lower filtration rate in failure arises from a decrease in filtration in all glomeruli and that the filtered load of sodium and water imposed upon the tubules therefore is greatly reduced. It is equally possible that filtration has ceased altogether in some glomeruli, filtration in the remainder being somewhat reduced, remaining unchanged or even increasing, depending upon the number of inactive nephrons. There is no evidence available in the literature to provide an answer to this question, but un-

anemia edema formation is occasionally seen.⁴⁹ It is prone to occur in pernicious anemia during return of the hematologic picture to normal. The renal blood flow has been found to be greatly reduced in this condition though glomerular filtration is not much affected.¹⁸ The intrarenal vasoconstriction appears to be but slowly reversible and in consequence a rise in hematocrit in response to therapy may lead to replacement of plasma by red cells in the unchanging volume of blood perfusing the kidney. The renal plasma flow and filtration rate may then fall as in the patient whose course is plotted in Figure 2. Edema formation under these circumstances may be attributed to the fall in filtration since glucose Tm is demonstrably normal and definite increase in glomerulotubular imbalance must develop. In the subject illustrated in Figure 2, however, edema did not appear. There was a slight gain of weight which persisted after complete recovery, probably as a result of improved appetite and diet. It is of great interest that in this patient and in one other¹⁸ edema did not form despite the fall in filtration and an unchanged (or augmented) intake of salt and water. It may be concluded therefore that an alteration in glomerular filtration of a degree similar to that usually observed in congestive failure is usually insufficient in itself to induce water and salt retention with edema formation. Although it should be emphasized that the change in filtration probably contributed importantly and may provide a necessary setting for this development, other factors must be implicated. Among these a relative augmentation of sodium reabsorption may play a role.

Tubular reabsorption of sodium is so large that small and scarcely detectable changes will produce large changes in the urinary output of sodium. It is an active process affected by the concentration gradient between blood and urine, by the presence of osmotically active materials in the filtrate and by various humoral agents.⁴⁰⁻⁵⁰ None of these factors is known to operate in failure although it has been

suggested^{51,52} that overproduction of anti-diuretic hormone by the posterior pituitary may occur. Recent work indicates that tubular reabsorption of water and salt is increased by elevation of the renal venous pressure. Since venous hypertension is

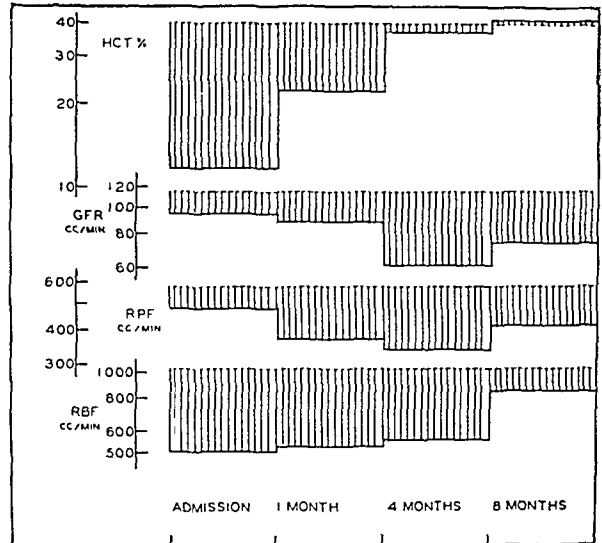


FIG. 2. Change in renal function during treatment of pernicious anemia. In E. M., a fifty-seven year old white female with pernicious anemia of about six months' duration, treatment with liver extract resulted in a return of the hematocrit (HCT) from 12 per cent to normal within four months. The reduction in renal blood flow (RBF) persisted for four months and may be attributed to intrarenal vasoconstriction which was slowly reversible. With improvement the glomerular filtration rate (GFR) and renal plasma flow (RPF), measured by the mannitol and sodium *p*-amino-hippurate clearances, respectively, fell from values somewhat lower than average normal (baselines) to abnormally low levels, apparently as a result of replacement of plasma by red cells with the rise in hematocrit. Despite the marked change in filtration in this patient there was no evidence of edema formation.¹⁸

prominent in failure, this response is undoubtedly of importance.

EFFECT OF ELEVATED RENAL VENOUS PRESSURE ON SODIUM AND WATER EXCRETION

It has been known for many years that obstruction to the venous outflow of the isolated kidney results in diminished output of salt and water,⁵³ but owing to the uncertainties and inaccuracies inherent in the heart-lung-kidney preparation clinicians have been reluctant to accept the implications of these observations. Renal

function studies in man have revealed a depression in sodium and water excretion when intra-abdominal venous pressure is raised to 20 mm. Hg by external abdominal compression with a pneumatic girdle.⁵⁴ Glomerular filtration and renal blood flow

blood flow, filtration rate and tubular activity apparently change chiefly as a result of the obstruction to urine outflow from a proportional number of nephrons. Subsequent work⁵⁵ has shown that the decrement in water output is associated

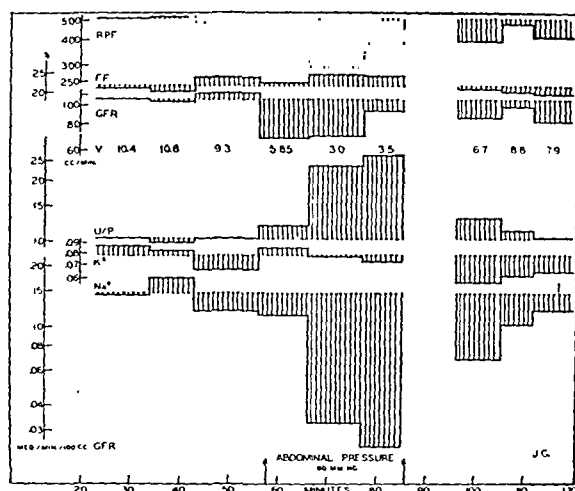


FIG. 3. Change in renal function during abdominal compression. J. G., a thirty-five year old white male with diabetes insipidus, was studied after re-establishment of diuresis on withdrawal of therapy. Clearance measurements of renal plasma flow (RPF), filtration fraction (FF), glomerular filtration rate (GFR), urine flow (V), and potassium (K^+) and sodium (Na^+) output were made before, during and after compression of the abdomen (between arrows) with a pneumatic belt under 80 mm. Hg pressure. Glomerular filtration rate and renal plasma flow decreased proportionately during compression of the abdomen so that the filtration fraction did not change. Urine flow fell greatly and mannitol concentration (expressed here as the ratio between urine and plasma concentrations (U/P)) increased, denoting increased water reabsorption relative to filtration. Sodium output expressed in terms of filtration rate ($\times 100$) fell off, but potassium output expressed in the same way did not change significantly. All values tended to return toward the average control values (baselines) after release of pressure. Similar results were obtained in studies of four other patients with diabetes insipidus and four normal subjects (from data of Mudge et al.⁵⁵).

are equally reduced in association with a proportionate reduction in active tubular mass as measured by diodrast and glucose Tm. Since all these values fall to approximately the same extent, there is no obvious glomerulotubular imbalance. Abdominal compression raises pressure in the renal pelvis as well as in the renal veins; and since the increment in venous pressure is sufficient to account for the reduction in

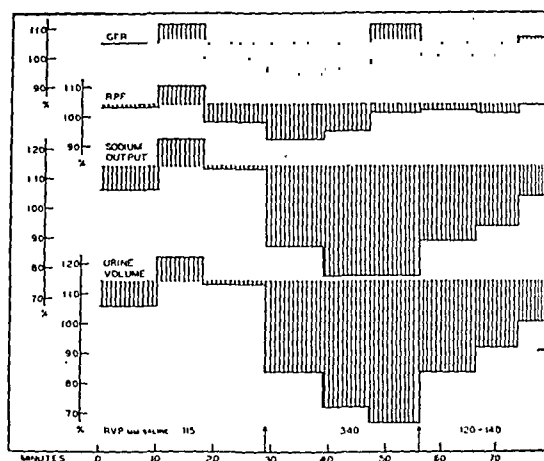


FIG. 4. Change in renal function in the dog during elevation of renal venous pressure. Values for glomerular filtration rate (GFR), renal plasma flow (RPF), urine flow and sodium output (mEq. per minute) of the left kidney are expressed here as percentages of the same functions determined simultaneously in the right or control kidney. During the control periods the left kidney put out 6 to 23 per cent more urine and sodium than the right, but with partial occlusion of the left renal vein and elevation of the left renal venous pressure from 115 mm. saline to 340 mm. saline (between arrows) there was a striking decrease in these values on the left over the right. During this period filtration and plasma flow did not change from the average control values (baselines) more than expected on the basis of spontaneous fluctuations. Sodium and water output of the two kidneys approached equality after the venous obstruction was removed (from data of Blake et al.⁵⁶).

with an even greater diminution in sodium excretion. The same response (Fig. 3) has been observed in five patients with diabetes insipidus following withdrawal of hormone therapy, indicating a direct effect upon the kidney rather than stimulation of the neurohypophysis. In all these studies the effect of obstruction due to elevated renal pelvic pressure cannot be separated from that of increased renal venous pressure.

Blake, Wégria, Keating and Ward⁵⁶ have investigated sodium and water excretion relative to glomerular filtration in the separate kidneys of dogs during unilateral elevation of renal venous pressure by partial

occlusion of one renal vein. Since renal function and urine flow change significantly only in the kidney subjected to increased venous pressure, humoral and neural activity appear to be unimportant. Sodium and water excretion are depressed when venous pressure exceeds 150 mm. saline with more and more depression at progressively higher levels. These changes occur without any clear-cut change in filtration and renal blood flow up to pressures of 400 mm. saline. (Fig. 4.) Filtration actually increased slightly on several occasions, definitely indicating enhanced tubular reabsorption. Renal blood flow did not decrease until venous pressure exceeded 400 mm. saline so that renal vascular resistance must have decreased in proportion to rise in venous pressure. Since filtration did not change, the resistance was probably lowered by passive distention of the renal veins, venules and peritubular capillary net. Such renal engorgement must be attended by an increment in renal interstitial pressure approximately equal to that in venous pressure and it may be supposed that engorgement influences water and sodium reabsorption by altering the gradient of pressure and flow of urine along the tubules—or possibly by changing the rate at which blood perfuses any given renal unit. These factors may also operate in conjunction with the vasoconstriction elicited by the erect position in causing the antidiuresis and lessened sodium output of orthostasis.^{57,58} Certainly elevated renal venous pressure within a range comparable to that observed during failure may adversely affect renal excretion of water and salt independently of humoral and vasomotor adjustments.

VENOUS DYNAMICS DURING FAILURE

The pressure in renal veins and elsewhere in the venous system derives from the complex interaction of the residual arterial pressure, the volume of blood held in the veins, the rate of blood flow into and out of the venous chambers, tissue tension and the "tonus" of the venous system as a whole.

In addition, skeletal muscular activity imposes further pressure changes and drives blood "uni-directionally" through valved vessels. Dynamically, the central venous reservoir is divided into two major compartments in which pressures may vary more or less independently.^{59,60} The pressure rises during expiration in the superior caval system (the supracardiac chamber) and falls in the inferior caval system (the subcardiac chamber). During inspiration the changes are reversed. Blood flows in opposite directions in these chambers under pressure gradients which are unrelated except that both are centered upon the right atrium. This independence is seen more strikingly during assumption of the upright position when pressure rises throughout the subcardiac chamber and falls almost to atmospheric pressure in the supracardiac chamber. The behavior of the total venous system cannot be characterized on the basis of pressures measured in a single peripheral vein.

In frank congestive heart failure all the veins are greatly engorged with blood and venous pressures are elevated throughout. The pressure in the right atrium may increase more than in the peripheral veins with a reduction in the pressure gradient.⁶¹ This phenomenon as well as the obvious fact of cardiac disease in the vast majority of cases implicates defective cardiac function as an essential element in the production of venous hypertension. But other factors including increased venomotor activity, redistribution of blood, venous compression and increased blood volume must be involved.

According to Starr and his co-workers⁶² the right heart may be severely damaged in experimental animals without altering venous pressure. Warren and Stead³ claim that an initial expansion in blood volume is necessary. In careful studies of the clinical course of patients with heart disease they have observed that a notable gain in weight may precede any detectable change in venous pressure. The validity of this observation depends upon isolated measure-

ments of pressures at rest in peripheral veins. In view of the complexity of venous dynamics such measurements appear to be inadequate. Moreover central and peripheral venous pressures rise sharply in patients with cardiac insufficiency and in animals with heart damage during exercise whereas little or no change occurs in the normal.^{63,64,65} In man increments in renal venous pressure observed during exertion in recumbency are further augmented on standing by the superimposed hydrostatic column of blood. Under these circumstances there is a striking decrease in water and sodium excretion.^{29,30} Hence abnormal elevations of pressure which are not detectable at rest may occur frequently during the course of each day and may be expected to have a profound effect upon not only the transcapillary balance of forces but also upon renal function. In addition, recent studies by Roos and Smith⁶⁶ indicate that venous pressure may rise in dogs immediately after myocardial injury, provided damage is sufficiently extensive and diffuse. The causes of immediate elevation in pressure are obscure and need not concern us here. It is sufficient to note that the elevation in venous pressure probably precedes edema formation and contributes to the pathogenesis of renal dysfunction.

Hypervolemia is probably important in accelerating the development of failure. In experiments of Landis⁶⁴ and of Roos and Smith⁶⁶ on animals with cardiac incompetence, intravenous injection of a small volume of saline solution or blood hastened and accentuated the change in venous pressure. Likewise, incautious administration of fluids intravenously to patients with cardiac disease will often precipitate decompensation.⁶⁷ Hence renal retention of salt and water is undoubtedly detrimental. It is not surprising that therapy designed to induce diuresis and to reduce blood volume is helpful. On the other hand, numerous studies^{64,68,69} in man and animals indicate that expansion of the blood volume within wide limits will not induce a persistent elevation in venous pressure unless there is

pre-existing cardiac disturbance. The development of congestive failure is to be regarded therefore as presumptive evidence of cardiac incompetence, even though anatomic evidence of a disorder of the heart may be lacking.

CONCLUDING REMARKS

On the basis of these considerations it is possible to set out an hypothesis which provides a reasonable explanation for renal dysfunction in heart failure. The place of the heart in this process scarcely needs reaffirmation and re-emphasis. Ample evidence is now at hand to support the view that cardiac output is insufficient for normal circulatory adjustments. The vasoconstrictive response to remedy this affects particularly the renal vascular bed even when blood flow to other tissues is increased, as in anemia. In consequence of the intrarenal vasoconstriction, renal blood flow and glomerular filtration rate are reduced with resultant impairment of kidney function. Remittent or persistent elevation of renal venous pressure also develops and acts to enhance tubular reabsorption of salt and water. Thus two changes, renal venous hypertension and intrarenal arteriolar constriction, operate simultaneously to produce retention of salt and water. It is quite likely that they contribute variously in different cases, but both appear to be necessary. This belief finds strong support in the fact that left ventricular failure may develop and persist in the absence of edema formation as long as venous pressure does not rise.

REFERENCES

1. FISHBERG, A. M. *Heart Failure*. 2nd Ed. Philadelphia, 1940. Lea & Febiger.
2. PETERS, J. P. The role of sodium in the production of edema. *New England J. Med.*, 239: 353-362, 1948.
3. WARREN, J. V. and STEAD, E. A., JR. Fluid dynamics in chronic congestive heart failure: an interpretation of the mechanisms producing the edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure. *Arch. Int. Med.*, 73: 138-147, 1944.
4. STARR, I. Our changing viewpoint about congestive failure. *Ann. Int. Med.*, 30: 1-23, 1949.

5. STEWART, H. J. and MOORE, N. S. The number of formed elements in the urinary sediment of patients suffering from heart disease, with particular reference to the state of heart failure. *J. Clin. Investigation*, 9: 409-421, 1930.
6. GOLDRING, W. Observations on the clinical application of the urine sediment count (Addis). *Am. J. M. Sc.*, 182: 105-114, 1931.
7. WHITE, P. D. Heart Disease. New York, 1945. The Macmillan Co.
8. HARRISON, T. R. Failure of the Circulation. Baltimore, 1939. The Williams & Wilkins Co.
9. SCHROEDER, H. A. Studies on congestive heart failure I. The importance of restriction of salt as compared to water. *Am. Heart J.*, 22: 141-153, 1941.
10. FUTCHER, P. H. and SCHROEDER, H. A. Studies on congestive heart failure. II. Impaired renal excretion of sodium chloride. *Am. J. M. Sc.*, 204: 52-62, 1942.
11. FARNSWORTH, E. B. Electrolyte partition in patients with edema of various origins. *Am. J. Med.*, 4: 338-342, 1948.
12. PETERS, J. P. and VAN SLYKE, D. D. Quantitative Clinical Chemistry. Vol. 1. Interpretations. Baltimore, 1931. The Williams & Wilkins Co.
13. SEYMOUR, W. B., PRITCHARD, W. H., LONGLEY, L. P. and HAYMAN, J. M., JR. Cardiac output, blood and interstitial fluid volumes, total circulating serum protein, and kidney function during cardiac failure and after improvement. *J. Clin. Investigation*, 21: 229-240, 1942.
14. MERRILL, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema. *J. Clin. Investigation*, 25: 389-400, 1946.
15. MOKOTOFF, R., ROSS, G. and LEITER, L. Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. *J. Clin. Investigation*, 27: 1-9, 1948.
16. BRIGGS, A. P., FOWELL, D. M., HAMILTON, W. F., REMINGTON, J. W., WHEELER, N. C. and WINSLOW, J. A. Renal and circulatory factors in the edema formation of congestive heart failure. *J. Clin. Investigation*, 27: 810-817, 1948.
17. SMITH, H. W. Lectures on the kidney. Lawrence, Kansas, 1943. University Extension Division, University of Kansas.
18. BRADLEY, S. E. and BRADLEY, G. P. Renal function during chronic anemia in man. *Blood*, 2: 192-202, 1947.
19. LAUSON, H. D., BRADLEY, S. E. and COURNAND, A. The renal circulation in shock. *J. Clin. Investigation*, 23: 381-402, 1944.
20. GIBSON, J. G. and EVANS, W. A., JR. Clinical studies of the blood volume. III. Changes in blood volume, venous pressure and blood velocity rate in chronic congestive heart failure. *J. Clin. Investigation*, 16: 851-858, 1937.
21. McMICHAEL, J. and SHARPEY-SCHAFER, E. P. The action of intravenous digoxin in man. *Quart. J. Med.*, 13: 123-135, 1944.
22. RICHARDS, D. W., JR. Cardiac output by the catheterization technique in various clinical conditions. *Federation Proc.*, 4: 215-220, 1945.
23. MYERS, J. D. and HICKAM, J. B. An estimation of the hepatic blood flow and splanchnic oxygen consumption in heart failure. *J. Clin. Investigation*, 27: 620-627, 1948.
24. BRANNON, E. S., MERRILL, A. J., WARREN, J. V. and STEAD, E. A., JR. The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. *J. Clin. Investigation*, 24: 332-336, 1945.
25. EDHOLM, O. G., HOWARTH, S. and McMICHAEL, J. Heart failure and bone blood flow in osteitis deformans. *Clin. Sc.*, 5: 249-260, 1945.
26. BURWELL, C. S. and DEXTER, L. Beriberi heart disease. *Tr. A. M. Physicians*, 60: 59-64, 1947.
27. HICKAM, J. B. and CARGILL, W. H. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J. Clin. Investigation*, 27: 10-23, 1948.
28. RILEY, R. L., HIMMELSTEIN, A., MOTLEY, H. L., WEINER, H. M. and COURNAND, A. Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. *Am. J. Physiol.*, 152: 372-382, 1948.
29. MERRILL, A. J. and CARGILL, W. H. The effect of exercise on the renal plasma flow and filtration rate of normal and cardiac subjects. *J. Clin. Investigation*, 27: 272-277, 1948.
30. SINCLAIR-SMITH, B., KATTUS, A. A., GENEST, J. and NEWMAN, E. V. Changes in the renal mechanisms of electrolyte excretion and the metabolic balances of electrolytes and nitrogen in congestive cardiac failure with exercise, rest, and aminophyllin. *Bull. Johns Hopkins Hosp.* (In press.)
31. STARLING, E. H. The Fluids of the Body. London, 1909. Archibald Constable and Co. Ltd.
32. MOKOTOFF, R. and ROSS, G. The effect of spinal anesthesia on the renal ischemia in congestive heart failure. *J. Clin. Investigation*, 27: 335-339, 1948.
33. RANGES, H. A. and BRADLEY, S. E. Systemic and renal circulatory changes following the administration of adrenin, ephedrine, and paredrinol to normal man. *J. Clin. Investigation*, 22: 687-693, 1943.
34. SMITH, H. W., ROVENSTINE, E. A., GOLDRING, W., CHASIS, H. and RANGES, H. A. The effects of spinal anesthesia on the circulation in normal, unoperated man with reference to the autonomy of the arterioles, and especially those of the renal circulation. *J. Clin. Investigation*, 18: 319-341, 1939.
35. MERRILL, A. J., MORRISON, J. L. and BRANNON, E. S. Concentration of renin in renal venous blood in patients with chronic heart failure. *Am. J. Med.*, 1: 468-472, 1946.
36. BURRILL, M. W., FREEMAN, S. and IVY, A. C. Sodium, potassium and chloride excretion of human subjects exposed to a simulated altitude of 18,000 feet. *J. Biol. Chem.*, 157: 297-302, 1945.
37. BERGER, E. Y., GALDSTON, M. and HORWITZ, S. A. The effect of anoxic anoxia on the human kidney. *J. Clin. Investigation*. (In press.)
38. WESSON, L. G., JR. and ANSLOW, W. P., JR. Excretion of sodium and water during osmotic diuresis in the dog. *Am. J. Physiol.*, 153: 465-474, 1948.

39. MUDGE, G. H., FOULKS, J. and GILMAN A. The effect of urea diuresis on the renal excretion of electrolytes. *Am. J. Physiol.* (In press.)
40. WESSON, L. G., JR., ANSLOW, W. P., JR. and SMITH, H. W. The excretion of strong electrolytes. *Bull. New York Acad. Med.*, 24: 586-606, 1948.
41. SHANNON, J. A. The control of the renal excretion of water. I. The effect of variations in the state of hydration on water excretion in dogs with diabetes insipidus. *J. Exper. Med.*, 76: 371-386, 1942.
42. SMITH, H. W. The excretion of water. *Bull. New York Acad. Med.*, 23: 177-195, 1948.
43. VERNEY, E. B. Absorption and excretion of water: the antidiuretic hormone. *Lancet*, 2: 739-744 and 781-783, 1946.
44. LEITER, L. The role of sodium chloride in the mechanism and treatment of congestive heart failure. *Bull. New York Acad. Med.*, 24: 702-719, 1948.
45. EARL, D. P., JR. Personal communication.
46. LEITER, L. Personal communication.
47. SMITH, H. W., GOLDRING, W., CHASIS, H. A., RANGES, H. A. and BRADLEY, S. E. The application of saturation methods to the study of glomerular and tubular function in the human kidney. *J. Mt. Sinai Hosp.*, 10: 59-108, 1943.
48. GOLDRING, W. and CHASIS, H. Hypertension and Hypertensive Disease. New York, 1944. The Commonwealth Fund.
49. VAUGHAN, J. M. The gain in body weight associated with remissions in pernicious anemia. *Arch. Int. Med.*, 47: 688-697, 1931.
50. LOEB, R. F. Adrenal cortex and electrolyte behavior (Harvey Lecture). *Bull. New York Acad. Med.*, 18: 263-288, 1942.
51. HAMILTON, W. F. Notes on the development of the physiology of cardiac output. *Federation Proc.*, 4: 183-195, 1945.
52. FARNSWORTH, E. B. and KRAKUSIN, J. S. Electrolyte partition in patients with edema of various origins. Qualitative and quantitative definition of cations and anions in cardiac decompensation. *J. Lab. & Clin. Med.*, 33: 1534-1544, 1948.
53. WINTON, F. R. Physical factors involved in the activities of the mammalian kidney. *Physiol. Rev.*, 17: 408-435, 1937.
54. BRADLEY, S. E. and BRADLEY, G. P. The effect of increased intra-abdominal pressure on renal function in man. *J. Clin. Investigation*, 26: 1010-1022, 1947.
55. MUDGE, G. H., BLAKE, W. D., ALPHONSE, P. and BRADLEY, S. E. Unpublished data.
56. BLAKE, W. D., WÉGRÍA, R., KEATING, R. P. and WARD, H. P. The effect of increased renal venous pressure on renal function. *Am. J. Physiol.* (In press.)
57. BRUN, C., KNUDSEN, E. O. E. and RAASCHOU, F. The influence of posture on the kidney function. 1. The fall of the diuresis in the erect posture. *Acta med. Scandinav.*, 122: 315-331, 1945.
58. KATTUS, A., SINCLAIR-SMITH, B., GENEST, J. and NEWMAN, E. V. The effect of exercise on the renal mechanisms of electrolyte excretion in normal subjects. *Bull. Johns Hopkins Hosp.* (In press.)
59. CLARK, J. H., HOOKER, D. R. and WEED, L. H. The hydrostatic factor in venous pressure measurements. *Am. J. Physiol.*, 109: 166-177, 1934.
60. WILKINS, R. W., BRADLEY, S. E. and FRIEDLAND, C. K. Circulatory adjustments to the head-down posture. *J. Clin. Investigation*, 25: 937, 1945.
61. RICHARDS, D. W., JR., COURNAND, A., DARLING, R. C., GILLESPIE, W. H. and BALDWIN, E. DE F. Pressure of blood in the right auricle in animals and man: under normal conditions and in right heart failure. *Am. J. Physiol.*, 136: 115-123, 1942.
62. STARR, I., JEFFERS, W. A. and MEADE, R. H., JR. The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease. *Am. Heart J.*, 26: 291-301, 1943.
63. SZEKELY, P. Venous pressure responses to exercise. *Am. Heart J.*, 22: 360-366, 1941.
64. LANDIS, E. M., BROWN, E., FAUTEUX, M. and WISE, C. Central venous pressure in relation to cardiac "competence," blood volume and exercise. *J. Clin. Investigation*, 25: 237-255, 1946.
65. BLAKE, W. D. and BRADLEY, S. E. Unpublished data.
66. ROOS, A. and SMITH, J. R. Production of experimental heart failure in dogs with intact circulation. *Am. J. Physiol.*, 153: 558-566, 1948.
67. RICHARDS, D. W., JR., CAUGHEY, J. L., COURNAND, A. and CHAMBERLAIN, F. L. Intravenous saline infusion as a clinical test for right-heart and left-heart failure. *Tr. A. Am. Physicians*, 52: 250-258, 1937.
68. ALTSCHULE, M. D. and GILLIGAN, D. R. The effects on the cardiovascular system of fluids administered intravenously in man. II. The dynamics of the circulation. *J. Clin. Investigation*, 17: 401-411, 1938.
69. YEOMANS, A., PORTER, R. R. and SWANK, R. L. Observations on certain manifestations of circulatory congestion produced in dogs by rapid infusion. *J. Clin. Investigation*, 22: 33-45, 1943.

Combined Staff Clinics

Ulcerative Colitis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. DANA W. ATCHLEY: The natural history of ulcerative colitis is so variable that it would be proper to question the validity of its existence as a single disease. However, the different patterns of pathology and course present sufficiently similar etiologic and therapeutic problems to justify their classification as a single entity. Moreover, the complications of all types have common features that support this unitary approach.

The gross pathology of this disease is less consistent than the microscopic picture. Any part of the colon may be involved in all degrees of severity; the ileum may participate; abscesses may form; and polyposis is a late feature of serious significance. The clinical picture is equally diverse. Some patients are extremely ill with high fever and great prostration; pain or bleeding may be intense or completely absent. Unpredictable remissions and relapses make the evaluation of therapy most uncertain.

The most satisfactory approach to the analysis of a disease is afforded by the presence of a specific etiologic agent. Amebiasis presents such a situation. The topic of this clinic is not in that pleasant category. No hypotheses as to etiology have stood the test of critical study. Felsen has written extensively incriminating the dysentery group of bacilli, arguing that most patients with ulcerative colitis have either a history of bacillary dysentery or are carriers of the organisms. The majority opinion disagrees with Felsen. Dysentery bacilli are found in only a small percentage of cases and treatment of this disease with chemotherapy found effective in true bacillary dysentery is without benefit.

Bargen of the Mayo Clinic isolated a diplococcus in ulcerative colitis but his work has been discarded by most workers in this field. As in every obscure condition, allergy has its proponents but again no consistent evidence as to its etiologic role has been collected.

When the etiology of a disease remains obscure, a clear understanding of its mechanism may be an excellent substitute. The etiology of constrictive pericarditis is rarely assured but the dynamics of its effects on the circulation are so clear that therapy can be intelligently planned. Once again we find a relatively barren field in ulcerative colitis. The reason for the remissions and for the variations in pathology are equally obscure. However, recent biochemical studies may offer a clue to one of the factors in the production of this disease. Dr. Meyer will discuss the general subject of the lysozymes and then Dr. Prudden will tell us of the application of this knowledge to ulcerative colitis.

DR. KARL MEYER: The word "lysozyme" was coined by Fleming in 1918. He lumped together under this name a variety of agents found very widely distributed in nature which lysed not only certain air-borne organisms such as sarcinae and some micrococci but also certain micro-organisms shown subsequently not to be affected by lysozyme but presumably by other enzymes.

Lysozyme, as isolated from egg-white, one of the richest sources of this enzyme, is a basic protein of low molecular weight. It was crystallized a few years ago by Alderton and his co-workers who showed the molecular weight to be 18,500 and the isoelectric

point to be at pH 10 to 10.5. Mammalian lysozyme is quite similar and is the most basic protein found in warm blooded animals thus far. However, this basic property is not essential to the lysozymes in general. There are acidic lysozymes which occur in the latex of a wide variety of plants but they have the same specificity as the basic lysozymes of egg-white, of tears and of the gastric mucosa or of stool with regard to both their action on micro-organisms and their chemical specificities. Lysozyme acts on susceptible organisms by destroying (through hydrolysis) a constituent, a mucopolysaccharide, of the bacterial cell wall. The cell thus acted upon autolyzes, leaving behind an empty shell, a picture which is familiar from electron microscope studies of the action of bacteriophage.

A few years ago we obtained this substrate in a highly viscous form from *Micrococcus lysodeikticus*, a sarcina and an air-borne staphylococcus, which also happen to be susceptible to lysozyme. This viscous mucopolysaccharide is composed of an acetylated amino sugar and a phosphorylated polyhydric alcohol, which means that this polysaccharide belongs to the class of mucic acid polysaccharides. Lysozyme lowers the viscosity of solutions of this polysaccharide by hydrolyzing the glucosidic linkage of the hexosamine. In our method the loss of viscosity is measured, and we define as one unit the amount of lysozyme which produces half viscosity in ten minutes under standard conditions.

Crystalline egg-white lysozyme contains approximately 1,300 of such units per mg. Human tears contain about 1,400 units, but the tear glands of domestic animals and laboratory animals have a very low lysozyme titer. It is not known whether this high lysozyme titer in the tears or tear gland is characteristic for man or not, but it is very low in the animals which have been studied.

We studied further the distribution of lysozyme in the mammalian body and found rather surprisingly high concentrations in the gastric mucosa of man and some

animals. The pyloric region of man has a lysozyme titer of about 350 to 400 units per Gm. wet weight while serum has a titer of less than 1 unit per cc.

We then studied the action of lysozyme on the alimentary canal of experimental animals, which Dr. Prudden will discuss. These experiments have been confirmed and elaborated upon by two groups, one at Cornell Medical College working on ulcerative colitis, and one in Chicago working on the experimental effect of the action of lysozyme in animal stomachs. Contrary to our belief that lysozyme acts by depolymerizing an unknown constituent of the surface mucus, Dr. Grossman in Ivy's laboratory believes that lysozyme acts on the cells rather than on the surface mucus. We have not succeeded in isolating the substrate acted upon by lysozyme in the alimentary canal, which is a rather important and necessary step in the whole investigation. The known acid and neutral mucopolysaccharides of the gastric mucosa are not affected by lysozyme.

Lastly, I want to tell you about a few experiments on the inactivation of lysozyme. Lysozyme as it occurs in the alimentary canal and egg-white is a basic protein. We expected that acidic detergents would inactivate it and this proved to be the case. We chose the alkyl sulfates, half esters of sulfuric acid with a straight fatty alcohol chain, from C_{12} to C_{18} , for this study and found increasing inactivation of lysozyme as the carbon number increased. For example the C_{12} compound, dodecyl sulfate, inactivates 15 to 25 per cent of crystalline egg lysozyme in 5×10^{-5} molar solution while the C_{16} and C_{18} , the hexadecyl and octadecyl compounds, inactivate 82 per cent. The C_{16} compound has another advantage over the lower carbon member substances in that it does not react so readily with proteins less basic than lysozyme, particularly the serum proteins.

DR. JOHN F. PRUDDEN: Time does not permit presentation of the rather large amount of experimental work that has gone into the attempt to demonstrate that lysozyme is the local agent initiating the

lesions of chronic ulcerative colitis. We can summarize the work which has been done here by a team consisting of Dr. Karl Meyer, Dr. Alfred Gellhorn, Dr. William Lehman and myself¹ by saying: (1) Lysozyme can, when present in high concentration, remove the surface mucus of any portion of the alimentary tract from the cardia to the anus by hydrolysis and depolymerization of an unidentified component of the surface mucus. (2) It will produce ulceration in the alimentary tract of dogs when fed orally in doses which are comparable to those found in humans with chronic ulcerative colitis. (3) The mean lysozyme content of human stools from chronic ulcerative colitis patients is about twenty-seven times that of normal stools. (4) The lysozyme content invariably falls with improvement. (5) The colitic mucosa shows a nine-fold increase in lysozyme content over normal mucosa. (6) The mean daily output of lysozyme in chronic ulcerative colitis is 168 times that of normals.

We believe that these observations indicate that lysozyme is the etiologic agent which locally initiates the lesions of ulcerative colitis although we are in accord with the hypothesis that the basic difficulty may be psychiatric in nature.

On the basis of these findings we have begun therapy with anti-lysozymes, as noted by Dr. Meyer, at the Presbyterian and Roosevelt Hospitals. Two agents have been employed therapeutically, nisulfazole (para-nitrosulfathiazole) and sodium hexadecyl sulfate.

Nisulfazole was introduced into the therapy of chronic ulcerative colitis by Dr. Ralph Major without knowledge of its anti-lysozyme effect. This property was discovered while screening compounds which had been reported effective in the therapy of the disease. This was the only agent exhibiting such anti-lysozyme activity to an appreciable extent. An inhibition of 42 per cent was noted in a concentration of

.0007 M. The mechanism of this inhibition is not yet understood.

Nisulfazole can be employed in 0.5 Gm. tablets or in 10 per cent suspension in pectin with oil of peppermint as a preservative. The former is for oral therapy, the latter for retention enemas and in occasional cases when it is desirable to pass a Miller-Abbott tube into the terminal ileum and administer the suspension through the tube.

I will not go into the details of oral therapy. By retention enema we give 100 cc. twice a day, once in the morning and once in mid-afternoon, and the patient lies in shock position from the time of his morning retention enema until supper time. He is up and about at other times. We give a low-residue, high-protein, high-calorie diet with vitamin supplementation. We make no effort to restrict particular foods unless there is undeniable evidence of allergy.

With oral therapy there are appreciable amounts of nisulfazole and sulfathiazole, its reduction product, in the blood. However, when administered by the Miller-Abbott tube technic and by retention enemas only traces are found.

Dr. Gellhorn treated twenty-one patients with chronic ulcerative colitis with nisulfazole, mostly with retention enemas. He noted remission in thirteen, equivocal responses in two and no improvement or progression in six. At Roosevelt Hospital we treated five patients with acute ulcerative colitis, with remission in four and no improvement in one. Statistically this is not dramatic but we believe that the worth of the drug is undeniable because of the extreme type of disorder treated. In several instances long-standing colitis has been arrested for the first time in years and the patient has given evidence of renewed vigor. In others what seemed to be a fatal downhill course seemed to be completely reversed. We have no data on the subsequent course of most patients treated with nisulfazole. The four treated at Roosevelt Hospital are in remission and have remained so up to nine months. That is a very short length of

¹ MEYER, K., GELLHORN, A., PRUDEN, J. F., LEHMAN, W. L. and STEINBERG, A. Lysozyme activity in ulcerative alimentary disease. *Am. J. Med.* 5: 496, 1948,

time, of course. The follow-up study of the rest is under way.

Despite our belief that nisulfazole is a good therapeutic agent, the fact that nine of twenty-six patients did not respond made a search for a better inhibitor desirable. Such an agent was found in sodium hexadecyl sulfate, which Dr. Meyer has described and which, as he pointed out, inhibits lysozyme *in vitro* much better than nisulfazole. However, it has affinity not only for the NH_3^+ groups of lysozyme but of all proteins. This reduces the effectiveness of the compound below the test tube level where lysozyme is the only protein present; therefore, when using this drug one should prescribe a low-protein diet. Our practice has been to give 540 mg. of sodium hexadecyl sulfate every four hours around the clock. The drug apparently produces initial nausea, watery stools and epigastric pain in the majority of patients. These have subsided within two or three days in most instances but the drug apparently has irritative as well as therapeutic effects in some cases.

Our experience with sodium hexadecyl sulfate has been very limited as yet. We have treated eleven patients with ulcerative colitis, with complete remission in seven; two patients were definitely improved but continued to have loose movements despite a marked decrease in frequency; and two (with the highest lysozyme outputs) failed to improve. Of the seven patients showing complete remission, three suffered relapses but two of these responded to lower doses taken at home; in the third case subsequent treatment has not yet been attempted because of limited supplies of the drug.

On the basis of this brief experience we believe that anti-lysozyme therapy is a hopeful method of treatment for this very distressing disease and deserves further trial.

DR. ATCHLEY: Is there any work on the influence of the emotions upon the lysozyme titer?

DR. PRUDDEN: Yes, there is. Grace, Seton, Wolf and Wolff at Cornell recently pub-

lished² observations they had made on individuals with ulcerative colitis under varying emotional circumstances. They noted a marked increase in the lysozyme concentration of the stool and colonic surface mucus of these individuals at times of psychic stress. The number of observations was quite small; however, they were convincing. If this work is now confirmed by a large number of such determinations, it will be a very important contribution. Dr. Karush and Dr. Stewart in this institution are also studying the same problem.

DR. WALTER STEWART: Our results are not really worth mentioning yet. All we have done is to follow lysozyme titers in patients as we have treated them. It is our belief that if they are disturbed the titer goes up, and if not disturbed the titer goes down.

DR. ROBERT F. LOEB: I think this might be of some interest. The stools of patients with mucous colitis have been studied by Dr. Prudden and Dr. Meyer, if I am not mistaken, and do not show any increase in lysozyme, is that correct?

DR. PRUDDEN: That is correct, but only three patients have been studied. I do not think it is conclusive.

DR. LOEB: It seems to me that it would be important to extend that study; because if we assume that mucous colitis is of psychogenic origin and one finds that there is not an increase in lysozyme, in contrast with the patients who have developed non-specific ulcerative colitis, one might have a means of differentiating the psychogenic mechanisms.

DOCTOR: Are the diarrheas of specific etiology associated with increase in lysozyme?

DR. PRUDDEN: The only specific diarrhea that we have had the opportunity to assay was a case of amebic dysentery. The lysozyme content was 33 units per Gm. of stool. The upper limit of normal is at 9. We have not had any opportunity to do runs on

² GRACE, W. J., SETON, P. H., WOLF, S. and WOLFF, H. G. Changes in lysozyme formation in the human colon in various emotional states. *Bull. New York Acad. Med.*, 24: 390, 1948.

typhoid or the bacillary dysenteries. Plans have been made to obtain this type of specimen in the near future.

DR. ATCHLEY: Is there any relation between the motility of the bowel, or the state of the stool, and the lysozyme content?

DR. PRUDDEN: As a check we gave castor oil and magnesium sulfate to a fairly large number of patients. We found that there was only dilution of the lysozyme although the output for twenty-four hours increased slightly. This rise did not approach the increase in colitis.

DR. ATCHLEY: There are in ulcerative colitis a certain number of lesions which occur in regions remote or apparently unrelated to the colon. I have asked Dr. Fischel to discuss these observations in the hope that they may throw some light on the underlying processes operating to produce this disease.

DR. EDWARD E. FISCHEL: In this clinic during the past few years a number of cases of ulcerative colitis have been observed with extra-gut lesions, frequently of a rather spectacular nature. Erythema nodosum, purpura and other skin lesions have been seen, as well as arthralgias of varying severity. Occasionally the diagnosis of rheumatoid arthritis has been made. In addition the history of a previous bout of rheumatic fever has been noted in a few patients. These phenomena have been described by several authors but their incidence is variable, depending in part upon how much attention is focused exclusively on the gut. Extra-enteric phenomena are rarely mentioned in the voluminous charts of these patients unless pronounced changes occur.

Erythema nodosum has been described in about 1 per cent of the large series at the Mayo Clinic but other skin lesions such as pyoderma are much more frequent. Arthritis has been said to occur in about 4 to 6 per cent of the cases of ulcerative colitis in various clinics. In this hospital Dr. James Coss has recently reviewed eighty-five cases in which the work-up and subsequent study were considered adequate. A high incidence

of arthritis was found. Nineteen patients or 22 per cent had some degree of arthritis at some time in their course. Five of these had the diagnosis of rheumatoid arthritis on their charts but subsequent follow-up in most of these showed a degree of improvement that is not compatible with the usual course of untreated rheumatoid arthritis. The arthritis possibly is related to secondary infection which occurs so frequently in ulcerative colitis. It is of interest that bacteremias and, notably, bacillary dysentery give rise to arthralgias and arthritis. Seventeen of the eighty-five patients here had skin lesions of the various types mentioned.

The question arises as to the relationship of ulcerative colitis to the extra-gut lesions. It appears unlikely that the same process which initiates the colitis, whatever that be, also causes the arthritis and skin lesions. More probably these lesions are secondary to the inanition and bacterial infection that result from ulcerative colitis.

As Dr. Atchley mentioned in his opening remarks, it has been suggested that a specific bacterium causes ulcerative colitis. It is well known that various infections may cause diarrhea even if they do not directly involve the gastrointestinal tract. Thus infection of the upper respiratory tract in children gives rise to that acute diarrhea which enjoys the paradoxical name of parenteral diarrhea. However, in ulcerative colitis no specific organism has been consistently identified. Infection appears to play a secondary role although it may be a very important one in the clinical course of the patient.

Where there is infection, particularly of an intermittent or chronic variety, it may be expected as a physiologic response on the part of the host that sensitization at distant sites occurs and histologic changes take place according to the pattern of the Arthus or tuberculin reactions, with variations depending upon the site of the reaction, e.g., the skin, around the blood vessels or elsewhere. Microscopic aggregations of acute or chronic inflammatory cells have been

demonstrated in many patients following infections with a wide variety of organisms. Such lesions impress us clinically, however, only when they are severe enough and superficial enough to become macroscopically visible. This is, of course, a variation of the old focal infection hypothesis but I need not point out that the infection in ulcerative colitis is hardly focal.

Allergic mechanisms have been thought to play a role in the development of ulcerative colitis, perhaps as they have been thought to play a role in almost any undefined disease. Gray and Walzer studied exteriorized segments of gut in monkeys and observed human colostomies and proctoscopies. The subjects were passively sensitized to an antigen such as peanut oil by the injection of serum from a sensitized individual, and the mucosa exposed to this antigen, either directly or by ingestion. A severe inflammatory reaction occurred. Erythema and a profuse outpouring of mucus took place. In some instances acute ulceration of the mucous membrane occurred. This has been taken as a rational basis for the search for food allergy in cases of ulcerative colitis and for the use of elimination diets in the management of this disease. Although it is known that food allergy may cause acute diarrhea, it is extremely unlikely that this is the underlying cause of all cases of ulcerative colitis inasmuch as elimination diets appear to have no greater or better effect than the customarily employed low-residue diets with non-irritating foods. However, allergy to the various bacteria invading the exposed surface of the colon is probably instrumental in contributing to the severity of an already established ulcerative lesion, both by local necrotizing action of the allergic type and by obstructing lymphatic return.

In summary, the extra-gut lesions of ulcerative colitis serve to focus our attention on the fact that this disease, with its inaction and almost constant secondary bouts of infection, involves many systems outside of the gut, either by direct metastatic infection, by increasing susceptibility to infection

or by a phenomenon of hypersensitivity. These secondary phenomena of infection, of necrotizing allergic reactions, may in turn augment the severity of the existing lesion.

DR. ATCHLEY: In the absence of a definite etiology or a completely comprehended mechanism one seeks forces that may influence the course of a disease non-specifically. For instance, in asthma certain patients are quite comfortable except when they are in an extremely dusty environment. These factors are not primarily etiologic but they effectively exaggerate the disease manifestations.

An example of this in ulcerative colitis is the effect of diet. An excess of roughage in the diet may represent an added burden for the inflamed gut and in certain cases is an important therapeutic consideration. An extraordinary case in this clinic tended to relapse during menstruation, with remissions in the intermenstrual intervals. After a long downhill course the ovaries were removed with spectacular benefit.

We come next to the most controversial and one of the most interesting aspects of the whole problem, namely, the influence of the emotions on ulcerative colitis. We know quite well that psychic trauma will apparently precipitate a relapse or increase the symptoms. There are many studies of the neurotic personalities found in these patients. Dr. Walter Stewart will discuss this field. I have told Dr. Stewart that if he prefers to classify the emotions as a specific etiological agent rather than as a factor influencing the course of the disease, we shall be very glad to have him do so and take the consequences!

DR. STEWART: The beginning of the psychiatrist's interest in the somatic aspects of medicine dates back to Walter Cannon's contributions concerning the effect of emotions on physiologic function. His studies started a type of psychophysiology. The effect of emotions on the gastrointestinal tract is, as you know, very great. This fact allowed the psychiatrists to get a toehold on this general subject and since then they have been doing some pretty fancy footwork

for which I have to bear the responsibility today.

The psychiatric contributions to the study of ulcerative colitis began in 1930 with a paper by Murray which was followed by a second paper later in the same year. He reviewed twelve cases of ulcerative colitis. He noted a dramatic relationship between emotionally traumatic experiences and the onset of disease twenty-four to forty-eight hours later signaled by bloody diarrhea. He also noticed that these patients were very dependent and emotionally infantile. From this he reasoned that since the infant's response to fear is diarrhea, perhaps that was the emotion affecting these patients. The marked dependency of the patients studied is illustrated by the fact that of seven male patients, six showed an unbreakable, strong, dependent tie to their mother. The seventh showed a comparable relationship to an older sister who acted as a mother substitute. None of the seven men were married.

The next paper was by Sullivan in 1936. He reported six cases studied with psychiatric technics and tried to outline the sort of personality that developed ulcerative colitis. Since then there have been many publications, the most outstanding of which are those of Daniels and Alexander.

I want to reiterate a point made by Dr. Atchley. When we elect to discuss a symptom such as bloody diarrhea, we may be dealing with a heterogeneous group when viewed from the point of etiology. Even in a group homogeneous from an etiologic point of view, we may be working with multiple etiologic factors. It then becomes not a question of one or another of the possible etiologic factors but a concatenation of many factors. In ulcerative colitis there may well be multiple causes that produce the disease, not just one etiologic agent. I think everybody agrees that this is a complicated disease and there is probably room for everybody in it.

Our present state of knowledge suggests that in about 75 or 80 per cent of the patients that we psychiatrists see it is

possible to elicit a fairly typical history of emotional problems which seem to play some role in the disease process. The evidence for this comes from three points. One is the precipitating factor, the emotionally traumatic experience that precedes the occurrence of the disease. The second is the similarity of the basic personalities of this group and of the type of adaptation to life which they show; and third is the fact that they give evidence of the presence of neurotic disturbances prior to the onset of their somatic illness.

I would like to deal with the third point first. Wittkower in 1938 published a report in which he studied the frequency of neurosis prior to the onset of the illness. He found that patients with ulcerative colitis had an extraordinarily high frequency of previous neuroses, well outside that of the normal population. This disproves the thesis often stated that neurotic manifestations in patients with chronic ulcerative colitis are secondary to their prolonged debilitating disease and consequent invalidism.

To understand the role of precipitating factors described as traumatic experiences, I would first like to list some of them. A patient has a fight with his mother and then develops ulcerative colitis, or he loses money and develops ulcerative colitis, or he gets married and then becomes ill. But, one might say, these experiences are ubiquitous. People are always fighting, losing money or getting married. This is true. But in order to understand the potency of these experiences you have to have some understanding of the type of personality on which these experiences operate.

As I suggested before, these are exceedingly dependent people. They have learned to exist by leaning on somebody else; so when a potential ulcerative colitis patient has a fight with his mother and if she is the one on whom he was leaning, this takes on extraordinary meaning to him. It would be hard for you and me to understand the significance of the experience to him. Similarly, if he is a dependent person and the loss of money threatens his security, that

can have catastrophic meaning to him. Or, if he marries or becomes a parent, that is a tremendous increase in responsibility and in a negative sense threatens his dependency. He is forced to make a more mature adaptation than he has made before. To generalize this, one can say that these experiences are a threat to the dependency relationship on which these people depend for their existence.

Now what I will try to do is to give you a sort of outline of the typical personality of the ulcerative colitis patient. You will probably never find all of these factors in any one patient and you certainly will find some patients that have none of them. When you come across a patient who has none of the characteristics that I am going to describe you might argue that I am therefore wrong. I would argue the exception proves the rule; mainly it is evidence of our incomplete understanding. The final word on this has not been written at all; just the opening chapters of it are beginning to be understood.

Typically, the father of the child who is later going to develop ulcerative colitis is likely to be aggressive, dominating, frequently abusive or brutal. The child is consequently overtly fearful. The mother is likely to be a dominating, coercive, possessive and overprotective person. The child has to decide early in life how to handle these two problem parents. Generally, he settles for keeping away from the father and being submissive to the mother. He can rely on her strength as long as he agrees to her terms. He elects to be submissive in order to achieve a dependency relationship. He becomes submissive and agreeable at the expense of any rebellion. In effect, he achieves security through loss of freedom.

These patients are generally of high intelligence. In one series, 80 per cent were found to have an I.Q. of 115 or above. They are generally physically immature. The men have high voices, generally little body hair. The women are small breasted and generally narrow-hipped. Not only are they both physically immature but also emotionally

immature. As I have described, they are dependent upon one of the parental figures, most frequently the mother. They are methodical, precise, neat, meticulous and overly clean. They do not think dirty thoughts nor use dirty language. They are of low energy, passive, self-centered or narcissistic and generally proud, hence sensitive. They are likely to brood or stew over an imagined insult. They generally do not marry at all, or if they do, they marry late after an indecisive courtship to someone who is older than themselves. They recreate the dependency pattern with their husband or wife. The outstanding emotion that is observable in these people is fear. It is a natural product of their submissiveness. They fear to lose the dependent relationship which they need of necessity to stay alive. They are generally tremulous, cautious, obsequious and cooperative. They try to please you but underneath this subservient quality it is easy to detect its opposite. They are likely to be critical, demanding and subversive. I think the two terms that describe it best are subservient but subversive. Their dreams are likely to be violent, which is another indication of the tremendous rage that is pent up inside of them. Even in their interests in daily life they show a morbid interest in murder and rape which gives an indication of their tremendous pent-up rage. Part of their fear that you see on the surface is the response to this unconscious rage which exists inside of them. They not only fear the loss of the dependency situation but they fear the threat that their own unconscious is to this dependency. The rage accumulates because of their submissive adaptation. Since they are not able to express anger, it accumulates inside of them. It becomes undue and chronic because it is not ever allayed and the theory at present is that it is discharged through the autonomic nervous system. For reasons we do not know, in these patients it hits the lower intestinal tract rather than the stomach or blood vessels and they develop diarrhea.

I wanted to mention briefly the analytic

contributions in this field. They seem bizarre and are often ridiculed. This is because they are difficult to understand unless you have had personal experience with the analysis of one of these patients. The analysts believe that one of the reasons the lower intestine is chosen to express this pent-up rage and fear is because in childhood the first fight that ever develops with this overprotective, coercive, dominating mother centers around the question of toilet training. The mothers are neat and meticulous and they try to get their babies clean early of course. It is a matter of prestige and also it is an economy of diapers.

The child who is forced to be submissive as a small baby in the question of feeding, completely at the mercy of his mother, for the first time feels his authority. He can either agree to be bowel-trained or disagree. Frequently they disagree and a tremendous, catastrophic fight or battle develops which the mother wins. The child is generally trained early, and from that time on has that traumatic event of childhood as a method of expressing indirectly his rage and fear.

In the few minutes left I will deal with the problem of psychotherapy. The simplest form of psychotherapy is reassurance. One may describe these people as having fear over rage; that is, manifest fear and sub-manifest or repressed rage. Therapy can act to reassure these people, reduce their fear and allow their rage to come through. So you get an emotional catharsis or ventilation, frequently directed first at mother figures, some distance from the mother, and moving toward the mother finally. Often they end up by being violently angry at the mother. By this time they are dependent upon the therapist who believes he has not done very much. This is the most frequent symptomatic cure from the psychosomatic point of view. The therapist substitutes himself for the mother. He is not as coercive; he is a little less dominating and not so possessive. From this dependency, he can draw back slowly with small amounts of independence interjected.

The problem of re-educating the patient out of the whole framework of dependence into the framework of independence where he becomes aware of his executive capacity is extremely difficult. The question of the desirability of analysis for these patients is unsettled. There is some evidence that analysis may be contraindicated. These patients are often very depressed when you see them with their illness. It is easy to explain this as secondary depression. Analytic evidence shows, however, that it precedes the onset of illness. Ulcerative colitis, unlike peptic ulcer, seems to be more closely related to the psychoses than neuroses, and analysis frequently uncovers material that the patient has not the resources to handle. In these cases, analysis may do more harm than good.

In closing I would like to read to you one paragraph which is a discussion taken from the journal, *Gastroenterology*. There were a group of people who talked over chronic ulcerative colitis and in the discussion later, Dr. Sullivan, to whom I referred earlier, said, "The observation with patients with ulcerative colitis suggests the following: What happened in 1929 on the 40th floor of the Empire State Building, a floor occupied only by brokers and bankers who were there when the stock market crashed? What happens to that dozen individuals up there? One of them steals from old women and children and goes to jail. Because he must continue to try to be a big shot and have plenty of money, he embezzles. Another one jumps out of the window because he cannot face life without money, and I understand you would have had to duck if you walked by there in 1929. A third turns to alcohol. What happens to the broker who has the peptic ulcer personality? There isn't a man in this room who has not seen that same misfortune befall patients with peptic ulcer. What do they do? They roll up their sleeves, go to work and make another million in six months or a year and of course, they get recurrences with hemorrhages or perforations. What happens on the 40th floor of

the Empire State Building to the man who has ulcerative colitis? He would never be there." He might have added he would have been home with his mother!

DR. ATCHLEY: The next step in the analysis of a disease is a consideration of the effects of the disease upon the individual who is so afflicted. In ulcerative colitis we find so many of these secondary complications that they can be mentioned only very briefly. Among the local effects are abscess, perforation, polyposis and carcinoma. The individual as a whole may develop malnutrition with genuine vitamin deficiencies; he may become anemic and occasionally dehydrated. Furthermore, the psychologic effect of this type of illness with its inhibition of normal life pursuits may set up a serious vicious circle. Treatment of these general secondary effects of the disease itself is sufficiently routine to require no further encroachment on our limited time.

The local complications of ulcerative colitis often require surgical intervention and in many instances it seems wise to consult the surgeon in relation to technics for interrupting the total downhill course of the disease. Dr. John Lockwood will present the surgical point of view.

DR. JOHN S. LOCKWOOD: I never like to be in the position of defending surgical treatment as opposed to medical treatment, which is the basis on which so much argument goes on in a disease of this type about which so little is known of etiology. Actually surgical treatment simply is carrying out operative procedures under circumstances in which the fullest possible advantage has been taken of everything beneficial in the category of medical treatment.

The use of surgery in ulcerative colitis is necessarily directed either toward attempting to reverse an otherwise hopeless situation by checking the progress of the disease, or to remove a hopelessly diseased structure which, if left in place, remains a threat to the further health and comfort of the patient. It is in that light that the use of surgical procedures in ulcerative colitis must be considered.

The efficacy of surgery obviously depends upon the stage of the disease at which the surgical procedure is carried out. There has always been a great deal of disagreement as to the timing of surgical intervention in ulcerative colitis. I am speaking now particularly of the acute case with a spiking temperature, massive diarrhea, rapid loss of blood, protein and electrolytes, and progressively downhill course. There has been a tendency on the part of some physicians to take an optimistic view in this situation, hoping for the remission which does sometimes occur with astonishing abruptness. The time they refer such a patient to the surgeon will depend in part upon their experience with a previous case or the strength of their faith in conservative measures. That makes the comparison of surgical results in different clinics very difficult.

Since a permanent ileostomy is to be avoided if possible, certainly no conscientious surgeon would advocate resorting to a surgical procedure in ulcerative colitis until he, as well as the physician, has been convinced that conservative measures had failed. However, I think we ought to recognize that now and for the indefinite future it is going to be necessary to resort to surgical procedures in cases which have failed to respond to other methods of treatment, however rational.

The first type of case in which I think surgery becomes practically an emergency procedure is the acute case with progressively rapid downhill course, with loss of blood, protein and electrolytes which has defied all efforts at correction. Just how long such a condition should be allowed to go on without surgical intervention is very difficult to define. Opinion in the recent past has been moving more and more toward earlier intervention with a limit of about seven to ten days for the really acute, fulminating episode. The only procedure which would be contemplated at such a time would be complete diversion of the intestinal current usually by ileostomy; although in the case of segmental involvement in which only the

rectum and sigmoid are involved, it may be possible to do a colostomy and thereby gain the advantage of colostomy over ileostomy. Under these circumstances ileostomy may be considered a desperate but sometimes unquestionably life-saving procedure. We have all seen patients who within a relatively few days of complete diversion of the fecal stream have shown subsidence of fever and of blood loss although they may continue to have purulent discharge from the rectum for many days or weeks thereafter. Ileostomy does make it possible to stop the progressive physiologic disintegration. Very likely this simply is the result of modifying the conditions as regard secondary infection in the colon. None of us believes that ileostomy is a direct attack on the etiologic factor of ulcerative colitis.

The other indications for surgical intervention, apart from the acute case, are the long persistence of subacute manifestations of the disease, with recurrent bouts of bloody diarrhea, inability of the patient to gain weight, inability to resume anything like a normal life. Under these circumstances the surgical procedure indicated is colectomy, either partial or total, depending upon the degree of involvement of the bowel. Usually colectomy means a permanent ileostomy.

Stenosis, shrinkage, scarring of the colon with the result that it loses its proper function is another indication for surgery, particularly since we know there is a certain incidence of carcinoma (estimates vary from 1 to 3 per cent) in these chronically infected colons. Finally, it is obvious that perforation and hemorrhage are other indications for emergency surgery in ulcerative colitis.

How successful an ileostomy is depends upon the patient's attitude; on the promptness and unremitting attention which the surgeon gives to the care of the skin; on the success with which the patient makes use of modern types of ileostomy bags which protect the skin and in many patients permit them to resume normal life; and on the degree to which the patient has responded

to his surgical treatment. Sometimes it is possible to close the ileostomy and to re-establish continuity of the intestinal current, probably in not more than 10 per cent of the cases. One recent contribution in this field from Johns Hopkins Hospital has been the successful performance of an anastomosis between the ileum and the anus itself, leaving the sphincter mechanism and providing a perineal ileostomy with natural sphincter function. It has been surprising that in the cases in which this operation has been done successfully, the patient develops what corresponds to a rectal pouch and is able to have normal stools.

In 1941, Elsom and Ferguson³ published the results of a careful follow-up study of fifty patients with ulcerative colitis. Dr. Elsom is associated with Dr. Miller in the Gastrointestinal Clinic at the University of Pennsylvania; Dr. Ferguson is a surgeon. They worked together as the physician and surgeon must do in the proper appraisal of results in this disease. In selecting their material they deliberately chose patients with severe disease, and we may take their word for it that they chose groups treated by medical means alone and those treated by medicine plus surgical intervention in a comparable fashion in order to yield comparable data. In this series of fifty patients twenty-three were treated with medical procedures alone. The mortality in the one- to twelve-year follow-up was 32 per cent in those treated by medical procedures alone whereas the mortality in the surgically treated group was 26 per cent. Of greatest importance is the appraisal of the state of health one to twelve years after operation, a period of observation which perhaps provides inadequate follow-up but enough to justify the authors' interpretations. In the medical group only two of the twenty-three could be considered to be asymptomatic; several were invalids. In the surgical group the great majority were stated to have had

³ ELSOM, K. A. and FERGUSON, L. K. Appraisal of medical versus surgical treatment of idiopathic ulcerative colitis. Follow-up data on 50 cases. *Am. J. Med. Sc.*, 202: 59, 1941.

good results. Only two of the twenty patients who survived said that if they had it to do again they would not have ileostomy. The other eighteen unequivocally stated that if they had to go through it again they would chose the ileostomy in order to be rid of the disability under which they formerly labored. All the results were classified either as fair or good in twenty of the twenty-seven surgically treated patients who had survived the follow-up period. The ability to work was also of interest. Only two of the medically treated patients had been able to resume their occupation whereas over half of those surviving ileostomy and colectomy had been able to return to their normal occupations. Of those who were not able to do their normal work there were none who could not do light work.

DR. STEWART: I should like to raise one question in connection with the report by Drs. Elsom and Ferguson. The fact that the medically treated group is made up of those that chose not to have surgery makes them questionable as valid controls. You wonder why they did not submit to surgery. Possibly it is a measure of the additional fear in which they live. This might lead to a less favorable prognosis and so the comparison of the two groups would be biased. Emotional factors do not seem to have been taken into account.

DR. LOEB: I would just like to express a word of caution in the appraisal of therapy in this disease. As Dr. Lockwood pointed out, remissions in ulcerative colitis are common and may be of very long duration. I do not think it is unusual to find patients who have remissions of anywhere from one to perhaps five or ten years' duration. On that account one has to be particularly careful with this group of patients, especially in view of the importance of the psychogenic factors which play a role when the patient feels that he is being helped by his doctor in any way whatsoever. By way of illustration, you will recall that for a number of years the reports from the Mayo Clinic in

relation to the vaccine of Bergen were most dramatic.

DR. GEORGE A. PERERA: Early in the disease the medical man will urge conservative treatment to which the surgeon will often agree. In the later stages of the disease, many surgeons believe that the process has become too advanced for the risks of an operative approach. Are there sufficient data on patients operated upon early in the course of the disease to justify a less conservative attitude at this point?

DR. LOCKWOOD: It would be my impression that the results of ileostomy would vary inversely with the duration of the disease; that an ileostomy done before advanced organic changes had taken place in the colon would be more likely to be successful than one performed late in the disease after extreme physiologic depletion and marked scarring of the colon had developed. Certainly ileostomy should not be performed in every patient who develops an acute bloody diarrhea. However, if the patient's condition continues to deteriorate from such a cause and if there is evidence of marked systemic reactions to the disease, one should not delay more than seven to ten days before resorting to ileostomy. This is a situation which calls for refined judgment and I doubt if there are sufficient statistics to provide a clearcut answer to the question.

DOCTOR: Dr. Lockwood, would you comment on surgical interruption of nerve pathways in ulcerative colitis, specifically vagotomy?

DR. LOCKWOOD: In connection with the possible role of the autonomic nervous system in this disease, there is an interesting experimental study going on now which has to do with the evaluation of vagotomy in the treatment of ulcerative colitis. Dr. Clarence Dennis of the University of Minnesota has now performed vagotomy in thirty patients with severe ulcerative colitis. Because it was recognized that this was a highly debatable procedure, only severe cases have been selected. In this series, many of whom have now been followed for periods of up to eighteen months, there has been no oper-

ative mortality. One patient is worse; four are no better and twenty-five are classified as definitely improved.

The rationale for this procedure is rather tenuous, based on the fact that if a pre- and post-ganglionic sympathectomy is performed to remove the abdominal ganglia, an acute ulcerative process follows in many instances, both in the experimental animal and in one or two instances in which it has been performed in man. In trying out vagotomy Dr. Dennis simply was applying the reverse of this mechanism. We have done three vagotomies here on two patients who had very active disease and on one with only subacute disease in which the main problem was complicating leg ulcers. These three patients are now all in remission. One has resumed his normal occupation working on a farm; one is asymptomatic as far as the colitis is concerned but is suffering with severe arthritis as a complication. Although our series here is too small to be of significance, the results of Dennis suggest the possibility that one might apply "psychotherapy with the scalpel" in a fashion similar to that which has been carried out in the treatment of peptic ulcer. Final results will be awaited with great interest.

DR. ALFRED GILMAN: If the autonomic nervous system is to be implicated in this syndrome, it seems to me a very simple procedure to take one or two patients and block off both the adrenergic and cholinergic nerves to the bowel with tetraethylammonium and find out what happens to the lysozyme titer and clinical state of the patient.

DR. PRUDDEN: We will try that.

SUMMARY

DR. FREDERICK K. HEATH: The manifold nature of the clinical picture of ulcerative colitis, from mild to severe; the admixture of other tissue responses such as dermatitis and arthritis; the tendency to important complications of anemia, malnutrition, abscess formation, perforation, polyposis and carcinoma; the lack of correlation between

symptoms and the presence of bowel lesions, and the ever present possibility of remission were discussed. The position was taken that the etiology of the syndrome was unknown and that multiple causes may exist. Infection was discarded as an initiating factor although it often plays a secondary role. The place of allergy is not clear but is rarely important. The significance of the emotions was emphasized. The usual patient with ulcerative colitis presents evidence of prior neurosis, has attacks after an emotionally upsetting event and exhibits a typical personality characterized by intelligence, immaturity, dependency, fear and well hidden rage.

Lysozyme was discussed as offering a possible clue to the mechanism of the intestinal phase of the syndrome. The enzyme in man is a basic protein of low molecular weight with the ability to destroy by hydrolysis a specific but not yet identified acid mucopolysaccharide of the intestinal mucus or mucosal cell. It is present in high concentration in the normal pyloric mucosa. The enzyme has been shown experimentally to be capable of denuding the mucosal surface of its protective layer of mucus and may thus initiate the ulcerative lesion. The mucosa and stools of patients with ulcerative colitis contain much larger amounts of lysozyme than in normal subjects or patients with other types of diarrhea. Further, the concentration in the stools of patients with ulcerative colitis varies with their emotional state and falls with improvement in symptoms.

The lysozyme hypothesis also offers a therapeutic approach. Thus it has been shown that nisulfazole and the alkyl sulfates inactivate the enzyme not only in the test tube, but in more than two-thirds of patients with severe ulcerative colitis treated with either of these substances improvement in symptoms and fall in the stool level of the enzyme have resulted. As yet insufficient data are available to permit definite conclusions.

The possible role of the autonomic nervous system in the syndrome as a mediator of

impulses necessary to activate the enteric mechanism, whether this be lysozyme or some other as yet unknown agent, was suggested by the experimental surgical trial of vagotomy.

More clearly defined perhaps is the conventional surgical approach to the disease. When deformity of the colon, polyposis or possible carcinoma exist, some type of resection is indicated. Infection, such as abscess or perforation with peritonitis, demands surgical care. Many individuals with long continued disease not responding to other measures come to surgery by default. Others with severe acute disease may be candidates for ileostomy or colostomy, depending upon the site of the lesions, early in their course. Good results have been reported in all of these instances

in a sizeable proportion of cases. The presence of an ileostomy has been a less serious problem when careful preoperative information and postoperative instruction and care have been given.

However, if surgery has been decided upon, it appears clear that it should be considered before it is too late. The ultimate mortality figures in surgically treated patients are no higher than in medically treated groups but surgical intervention may become beyond the tolerance of a severely debilitated patient.

Yet the prospect of remission which remains utterly unpredictable as to its occurrence and duration continually beclouds all investigative and therapeutic efforts so that evaluation of data remains difficult.

Clinico-pathologic Conference

Anorexia, Weakness, Prostration and Death*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, O. H., (B. H. No. 161061), a fifty-one year old, white, married, carpenter's helper, was admitted to the Barnes Hospital on July 7, 1948, in a terminal state. No history could be obtained from him and the following limited information was given by his wife: The patient had apparently enjoyed perfect health until two months before entry at which time he noted the onset of anorexia. Concomitantly, painful bleeding hemorrhoids appeared and several weeks later the patient consulted a physician who performed a hemorrhoidectomy in his office. Shortly after the operation the patient returned to work but anorexia and rectal pain persisted and progressive weakness was noted. After working for one week the patient was unable to continue.

He again consulted his physician who told the patient that he probably had "cancer of the stomach," and the patient went to the Out-patient Clinic of the Barnard Free Skin and Cancer Hospital. Examination there revealed an ulcer 2 by 2 cm. in the posterior portion of the anus at the mucocutaneous junction which was said to have resembled a squamous cell carcinoma. Upon digital examination a questionable soft tissue mass was felt on the anterior wall of the rectum. He was advised to enter the hospital for further study but no bed was available; therefore, his name was placed on the waiting list. He began to have pain in the upper mid-abdomen which was constant but unrelated to position, movement or ingestion of food;

at no time was the pain severe. Anorexia and weakness increased, however, and in the week prior to admission during which the patient was able to take practically no food a state of prostration developed. In the two months he was ill he had lost approximately 25 pounds, but no change in the color of his skin had been noted nor had he had any diarrhea. On the day of admission he was brought to the Washington University Clinics and immediately sent into the hospital.

At the time of entry his temperature was 38.2°C., pulse 80 and respirations 32; his blood pressure was unobtainable. The patient was extremely cachectic and appeared ten to fifteen years older than his stated age. He was markedly dehydrated and hic-coughed frequently. His skin was brown and dusky in color but there was no localized pigmentation. The mucous membranes of the conjunctivae were pale; the sclerae were muddy. The lips were slightly cyanotic and there was minimal pigmentation of the mucous membrane of the lower lip. The pupils reacted normally to light and accommodation and the optic fundi appeared normal. The mouth was edentulous and the tongue dry. The trachea was in the midline. Examination of the lungs revealed them to be clear to percussion and auscultation. The heart was not enlarged to percussion. The rhythm was regular; there were no murmurs but the sounds were distant. The abdomen was flat and tense. No masses could be felt and there was no edema. No generalized glandular enlarge-

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

ment was noted. Because of the patient's extremely critical condition further examination was deferred in order that treatment might be begun.

Limited laboratory data were as follows: Hemoglobin, 15 Gm. per cent; white blood cell count, 7,000; urinalysis: no specimen could be obtained. Blood chemistry: non-protein nitrogen, 42 mg. per cent; sugar, 214 mg. per cent (blood obtained after administration of intravenous glucose); chloride, 80 mEq./L.; total protein, 7.1 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 3.8 Gm. per cent.

As soon as the patient reached the ward 5 per cent glucose in saline was administered intravenously into one arm and plasma into the other. The pulse seemed to become stronger but after approximately 500 cc. of glucose and 250 cc. of plasma had been infused the patient suddenly had a convulsion and expired.

CLINICAL DISCUSSION

DR. W. BARRY WOOD, JR.: I should like to begin our discussion today by asking if any student cares to commit himself in regard to the diagnosis.

MR. DONALD GREAVES: In view of the marked anorexia and the physical findings at the time the patient was examined at the Barnard Hospital, I should like to suggest carcinoma of the rectum with metastases to the liver. Such striking anorexia often indicates liver involvement.

DR. WOOD: Does marked anorexia suggest an hepatic lesion to you, Dr. Shank?

DR. ROBERT E. SHANK: Yes, I would agree that anorexia frequently is an important symptom of hepatic disease.

MR. LAURENS WHITE: I think that the patient had adrenal insufficiency, the severe, rather acute anorexia being explained by the low serum chloride.

DR. WOOD: What pathologic lesions should be considered?

MR. WARREN FELTON: Tuberculosis, idiopathic atrophy or carcinoma might have caused adrenal failure.

DR. WOOD: How would carcinoma lead to adrenal insufficiency?

MR. FELTON: It would of course have had to involve both adrenals.

DR. WOOD: If there are no other suggestions, we shall consider carcinoma of the rectum with metastases to the liver and adrenal insufficiency of a cause as yet undefined. Dr. Scheff, you will remember that this patient, in addition to his anorexia, was bothered by hemorrhoids. Is there any connection between these two complaints?

DR. HAROLD SCHEFF: I do not think so.

DR. WOOD: If this patient had come to your office with these complaints, would you have recommended hemorrhoidectomy?

DR. SCHEFF: In such a situation as this I would have first obtained a complete gastrointestinal x-ray series. Further, stool examinations should have been done for occult blood and parasites. The soft tissue mass which was described on the anterior wall of the rectum when the patient was examined at the Barnard Hospital was probably not significant. Had it been a carcinoma the mass should have been very hard and indurated.

DR. WOOD: Then you would have instituted more complete studies because of the fact that his presenting complaints, particularly the anorexia, were not explained satisfactorily by the presence of hemorrhoids.

DR. SCHEFF: That is correct.

DR. WOOD: I think it is very important for us to emphasize this point since the most obvious operable lesion does not necessarily represent the patient's major problem. Dr. Duden, would you discuss the anal ulcer which this patient had and comment on the etiology of ulcers in the lower portion of the gastrointestinal tract?

DR. CHARLES W. DUDEN: A very common type of anal ulcer in patients with hemorrhoids is that which arises as a result of local venous thromboses. Ulcerative colitis must also be considered.

DR. WOOD: Is carcinoma a possibility?

DR. DUDEN: The site involved here is not common for carcinoma of the rectum. This type of lesion which was located at the

mucocutaneous junction brings to mind an epithelioma.

DR. WOOD: This patient apparently did not develop the ulcer until after hemorrhoidectomy. Is such a sequence of events common after that operation?

DR. DUDEN: Interestingly enough, the converse may hold; that is, an ulcerative lesion about the rectum may lead to thromboses of the hemorrhoidal vessels, and not infrequently hemorrhoidectomy is performed without the basic lesion having been recognized. I would not be at all surprised if such were the case here.

DR. WOOD: Dr. Kenamore, do you believe that this patient had a malignant lesion of the lower bowel?

DR. BRUCE D. KENAMORE: I think it possible but unlikely. Although he was examined in the out-patient department of the Barnard Hospital where clinicians, who have had a wide experience with carcinoma, suggested that diagnosis, the entire clinical picture does not seem consistent with such an interpretation. I should like to point out in passing that the hemorrhoidectomy was performed without due consideration of the patient's general status.

DR. WOOD: Should hemorrhoidectomy be done in office practice?

DR. KENAMORE: I believe strongly that it should not.

DR. WOOD: Is it not done frequently by physicians in their offices?

DR. DUDEN: Yes, that is unfortunately true.

DR. WOOD: Dr. Kenamore, since you think that this patient probably did not have carcinoma of the lower bowel, can you offer any alternative suggestion?

DR. KENAMORE: I believe that the ulceration was more suggestive of tuberculosis or possibly amebiasis. The history is not in keeping with amebiasis but occasionally the course may be atypical.

DR. SCHEFF: It is difficult for me to believe that this man developed the anal ulcer immediately after his hemorrhoidectomy; in that event, he certainly would have had more difficulty postoperatively.

DR. WOOD: Do you think he may have had carcinoma?

DR. SCHEFF: No, an inflammatory lesion such as tuberculosis seems more likely to me.

DR. WOOD: I heard Dr. Hunter say before the conference that he had worked out a complete diagnosis for this case.

DR. THOMAS H. HUNTER: I have been "scooped" by one of the students. I had in mind the suggestion, already put forth, that this patient had a malignant lesion of the gastrointestinal tract with metastases to the liver and to both adrenal glands, with resultant adrenal insufficiency. He had marked anorexia and weight loss, both of which point to an upper gastrointestinal neoplasm. I agree that most of the evidence does not favor carcinoma of the lower intestine.

DR. WOOD: Exactly what site in the gastrointestinal tract did you have in mind?

DR. HUNTER: The stomach particularly.

DR. WOOD: Does that possibility appeal to you, Dr. MacBryde?

DR. CYRIL M. MACBRYDE: I think it is a good one; it must be remembered, however, that carcinoma with adrenal failure is very rare whereas tuberculosis of the adrenals is quite common. Next to tuberculosis I should think of other forms of infection. The fact that this patient became much worse soon after hemorrhoidectomy brings to mind the possibility that he may have developed infection at the operative site which subsequently spread to involve the adrenals.

DR. WOOD: Then in addition to Dr. Hunter's suggestion of metastatic carcinoma of the adrenals you would add tuberculosis or pyogenic infection. Do you believe that this patient had true adrenal insufficiency?

DR. MACBRYDE: He certainly died in a state that simulated adrenal insufficiency. He was severely dehydrated, in shock and hypochloremic. All of these findings are compatible with acute adrenal cortical failure.

DR. WOOD: Dr. MacBryde, what further data would be helpful had they been available? It is clear that this patient died so

soon after entry that complete studies were impossible.

DR. MACBRYDE: Blood potassium and sodium determinations would certainly have been of value.

DR. WOOD: Would not the carbon dioxide combining power and the serum chloride, taken together, have been of some value in a situation such as this?

DR. MACBRYDE: I would prefer to have sodium and potassium determinations.

DR. WOOD: I agree that those two would have been most valuable; on the other hand, measurement of carbon dioxide combining power is relatively simple to carry out and that value, taken with the serum chloride, enables one to estimate the blood sodium as a first approximation. When the flame photometer becomes readily adaptable for routine clinical determinations, it will serve as a most valuable aid in cases such as this. Dr. Moore, would you comment on the blood count in Addison's disease. Would a differential count have been helpful?

DR. CARL V. MOORE: A relative lymphocytosis is seen in adrenal insufficiency but such a change is not diagnostic; of more value possibly is the eosinophil determination which has recently been described by Thorn and his co-workers.¹ In a moribund patient, however, none of the diagnostic studies is very reliable.

DR. WOOD: Gastrointestinal malignancy is one of the diagnoses under consideration. Do you believe that hemoglobin of 15 Gm. is consistent with such a lesion?

DR. C. V. MOORE: The patient was markedly dehydrated. If he had survived until adequate hydration was achieved, his hemoglobin might actually have been only 10 Gm. instead of the 15 Gm. recorded.

DR. WOOD: Dr. Moore's answer indicates how carefully one must evaluate all laboratory data, particularly in a case such as this one. Although the blood sugar was re-

corded as 214 mg. per cent, we cannot be certain that this patient on admission was not indeed hypoglycemic, since he received an infusion of glucose before the blood sugar determination was performed. And now Dr. Moore points out that the hemoglobin of 15 Gm. per cent may well represent an apparent rather than a real value in view of hemoconcentration. Laboratory data may be most misleading unless properly evaluated in the light of the particular circumstances under which they are obtained.

STUDENT: I should like to know if the rapid downhill clinical course is compatible with a diagnosis of carcinoma of the body of the pancreas.

DR. DUDEN: I have never seen a patient with carcinoma of the pancreas fail as rapidly as this man did.

DR. WOOD: The fulminating nature of this man's illness favors adrenal insufficiency which may progress very rapidly indeed. Before we finish our discussion of the blood chemical findings I think it would be well to point out that the electrolyte changes might have been due to the fact that the patient had been vomiting. The electrolyte changes in Addison's disease may be simulated by the vomiting of prolonged pyloric obstruction. However, Gamble has compared the electrolyte changes in pyloric obstruction and in Addison's disease and has shown that there are significant differences.² For example, in Addison's disease the total base is depressed whereas the total base is not significantly depressed in pyloric obstruction. The carbon dioxide combining power, which was not determined here, would have been of value in differential diagnosis since in excessive vomiting due to pyloric obstruction the carbon dioxide combining power is often elevated whereas in Addison's disease it is decreased.

DR. ROBERT J. GLASER: I should like to ask whether the lesion in the rectum was described at the time that the patient was

¹ THORN, G. W., FORSHAM, P. F., PRUNTY, F. T. G. and HILLS, A. G. A test for adrenocortical insufficiency. The response to adrenocorticotrophic hormone. *J. A. M. A.*, 137: 1005, 1948.

² GAMBLE, J. L. *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid*. 5th ed. Cambridge, 1947. Harvard University Press.

admitted to this hospital. Was a rectal examination done?

DR. WOOD: Because this patient was in a terminal state when he entered the hospital, a complete examination could not be done. Dr. Chernoff, do you have any information in answer to Dr. Glaser's question?

DR. AMOZ I. CHERNOFF: No, I do not. As you have stated, because of the patient's extremely critical condition, the rectal examination was omitted.

DR. I. JEROME FLANCE: I think it would have been very unusual for the anal ulcer to have been due to carcinoma in view of the fact that this patient had no symptoms two months prior to his death. Similarly, in regard to tuberculosis, patients who have tuberculous ulcers of this size at the mucocutaneous junction of the rectum and anus in general have widespread tuberculosis involving other organs and exhibit signs of systemic illness over a longer period of time than did this man.

DR. KENAMORE: I would agree with Dr. Flance's comments. I have never seen a tuberculous ulcer associated with carcinoma but they are reported. There are, however, occasional cases of gastrointestinal tuberculosis apparently unassociated with systemic tuberculosis, just as in Addison's disease there may be no pulmonary tuberculosis.

DR. WADE: I do not think proper cognizance has been taken of the total protein, albumin and globulin determinations. The globulin was definitely elevated and that finding, in combination with hemorrhoids, anorexia and weakness, is compatible with a diagnosis of cirrhosis of the liver. Further, patients with cirrhosis may die in as short a time as this patient did. Despite the fact that some of the blood chemical findings suggest adrenal insufficiency, it is not particularly unusual for a patient with rapidly progressive cirrhosis to exhibit a similarly rapid downhill course, with a clinical picture suggesting adrenal exhaustion.

DR. WOOD: How many patients with cirrhosis have you seen die as rapidly as this man did without jaundice?

DR. WADE: Not many, but jaundice is often not severe in advanced cirrhosis and the statement was made here that this patient did have muddy discoloration of the sclerae.

DR. WOOD: Dr. Chernoff, did you think that the patient was jaundiced?

DR. CHERNOFF: I was certain he was not jaundiced but his skin color was not normal. It was brownish-yellow and I can best describe it as being of a coppery cast.

DR. WOOD: Dr. Taussig, does this picture suggest cirrhosis of the liver to you?

DR. BARRETT L. TAUSSIG: Cirrhosis is a possibility but it is difficult for me to understand how a patient without an alcoholic history could die from liver failure in two months after being apparently perfectly well.

STUDENT: I should like to know whether the albumin and globulin values are consistent with the diagnosis of Addison's disease.

DR. WOOD: The globulin was 3.8 Gm. per cent and the albumin 3.3 Gm. per cent. Are such values compatible with a diagnosis of adrenal insufficiency, Dr. MacBryde?

DR. MACBRYDE: They are certainly not characteristic of Addison's disease.

DR. WOOD: Would chronic infection explain them, Dr. Harford?

DR. CARL G. HARFORD: Chronic infection is often associated with hyperglobulinemia. Among the chronic infections one must certainly include tuberculosis.

DR. DUDEN: It seems conceivable to me that a less common type of tumor may have been present here. A rapidly growing neoplasm such as melanosarcoma would be consistent with a rapid downhill course and widespread metastases through the abdomen which conceivably could have involved both adrenals. I think whatever type of neoplasm he had, if indeed he had one, involved both adrenals.

DR. VIRGIL SCOTT: Why did the patient have a convulsion?

DR. MACBRYDE: One of the manifestations of acute adrenal insufficiency is disturbance in the central nervous system.

Many patients with Addison's disease actually die in epileptiform attacks, presumably on the basis of hypoglycemia.

DR. SCHROEDER: In view of the fulminating course in this case I should like to ask Dr. MacBryde if he does not think that tuberculosis is an unlikely cause of the adrenal failure.

DR. MACBRYDE: In many patients with adrenal insufficiency tuberculosis is not recognized until postmortem examination. I do not believe that the course of the adrenal insufficiency is particularly helpful in determining its cause.

DR. JOSEPH C. EDWARDS: I should like to ask the gastroenterologists to comment on the relation of diarrhea to gastrointestinal malignancy.

DR. DUDEN: Diarrhea is found in association with carcinoma of the rectum in approximately 18 to 20 per cent of the cases but more commonly constipation is seen. Those figures include carcinoma of the sigmoid and descending colon as well. Diarrhea is much more frequent when the malignancy involves the cecum and ascending colon but it certainly does not occur in over 50 per cent of those patients.

DR. WOOD: I should like to summarize the suggestions made by the students and by the staff before Dr. Moore presents the pathologic findings. If I sense the opinion of the group correctly, most of the staff members favor acute adrenal insufficiency caused by a lesion in the adrenal glands, presumably on the basis of tuberculosis or some other infection. The possibility of gastrointestinal malignancy with metastases to both adrenals has also been advanced as a cause of the adrenal insufficiency. The etiology of the anal ulcer remains obscure. The final clinical diagnoses made by the house staff at the time of the patient's death were as follows: ?adrenocortical hypofunction; ?neoplasm of unknown site.

Clinical Diagnoses: Acute adrenal insufficiency, ?due to tuberculosis or other infection; ?gastrointestinal malignancy with metastases to both adrenals; ?tuberculous

ulcer of the mucocutaneous junction of the anus.

PATHOLOGIC DISCUSSION

DR. F. BERTOLI: Advanced emaciation, pallor and a diffuse grayish brown discoloration of the skin were observed at the time of autopsy. No ulcerations were present on the skin surface.

Both pleural cavities were obliterated by dense fibrous adhesions over the superior portions of the upper lobes of the lungs and on each side there was a small amount of clear, straw-colored fluid. The lungs weighed 640 Gm. Upon section of the right lung numerous extensive areas of caseation, marked fibrous thickening of the interlobar stroma, grayish pink, rubbery parenchyma and scattered miliary tubercles throughout the upper lobe were exposed. The middle and lower lobes contained numerous foci of caseation and round, grayish yellow, gritty, calcified nodules measuring 1 or 2 mm. in diameter. A moderate amount of frothy fluid was present in the remaining parenchyma.

The tracheobronchial and bronchopulmonary lymph nodes were enlarged, black and edematous with small caseous and calcified nodules. A secondary branch of the pulmonary artery leading to the upper lobe of the right lung was partially obstructed by a grayish red thrombus firmly attached to its wall. The left lung contained similar but less advanced pathologic changes.

The heart which weighed 280 Gm. was of normal size and appearance.

The peritoneal cavity contained a small amount of clear yellow fluid and was free of adhesions. The spleen was slightly enlarged, weighing 200 Gm. The capsule was smooth and taut, and the pulp was abundant, dark red and firm; a few scattered calcified nodules 1 mm. in diameter were noted and the follicles were prominent. The liver weighed 1,950 Gm. The peritoneal surface was smooth and glistening and the cut surface smooth, firm and reddish brown with a prominent lobular pattern. The

kidneys, which weighed 180 Gm. each, were slightly granular on their cortical surfaces.

The adrenals were approximately three times normal size; the right weighed 26.5 Gm. and the left 38 Gm. They were covered by thick fibrous capsules. On section each presented a smooth, grayish yellow, firm, rubbery surface with dark red streaks and blotches.

The stomach, duodenum and pancreas were not remarkable. The distal portion of the ileum contained a deep, oval ulcer in the mucosa 2.5 mm. deep; it had thick elevated borders which were studded with small tubercles and its base was dark red and covered with grayish yellow debris. The ulcer extended through the muscularis to the serosa which was likewise studded with small tubercles arranged in a linear pattern along the course of the lymphatics. In the adjacent mucosa and in the mucosa of the cecum there were numerous shallow ulcerations measuring 1 cm. in diameter with tiny tubercles about their borders. The corresponding mesenteric lymph nodes contained foci of caseation and some were replaced by a tough, grayish yellow tissue. White streaks accompanied by tubercles could be traced across the mesentery from the intestine to these nodes.

The bladder and prostate were not remarkable. The right seminal vesicle was moderately enlarged and had a gray, thick wall which contained abundant loculated yellow, thick, granular material. The left seminal vesicle was not unusual. The vasa deferens and testes were not remarkable.

The brain was not examined. The sternal, costal and vertebral bone marrow were not remarkable.

DR. ROBERT A. MOORE: On the basis of the gross findings, it seemed apparent there was tuberculosis involving particularly the lungs, intestines, right seminal vesicle and adrenals. When, however, Dr. Margaret Smith reviewed this case shortly after the autopsy was performed, her astute knowledge of gross pathology enabled her to recognize that there were atypical

changes in the adrenal glands; they were too yellow and their consistency was rubbery rather than friable as is the case in tuberculous caseation. Consequently, a frozen section was ordered and an additional very interesting suspected diagnosis was immediately confirmed. The first section (Fig. 1) is from a paraffin block prepared later from the same tissue as the original frozen section. It represents all the adrenal gland which remained. From this and other sections it seems probable that 90 to 95 per cent of the adrenal cortex had been destroyed. This photomicrograph shows the edge of one of the foci of necrosis; about these foci there were large macrophages but no true tubercles, epithelioid cells or giant cells. With higher magnification (Fig. 2) it can be seen that these large macrophages were filled with round organisms with surrounding halos. The appearance, size and location of these organisms was so typical the diagnosis of histoplasmosis of the adrenal glands was established.

I want to point out that the diagnosis of histoplasmosis was not made unequivocally by Dr. Smith, but the gross appearance of the adrenals aroused her suspicions and led to the prompt search for some other diagnosis than tuberculosis. I emphasize this approach first to give credit to Dr. Smith for having suspected the correct diagnosis and, secondly, to reiterate what I often tell the students and staff, namely, that there is still a science of gross pathology. One does not need a microscope to make every diagnosis.

Despite the hours which had elapsed from the time of autopsy till the frozen section was prepared, material was taken from the adrenal in an attempt to culture the organisms; even in the face of the gross contamination that had occurred Dr. Parker Beamer was able successfully to isolate typical cultures of the fungus.

Despite this fascinating and rather startling finding, it must not be forgotten that most of the lesions were of a different nature. Figure 3 is from the lung and presents a

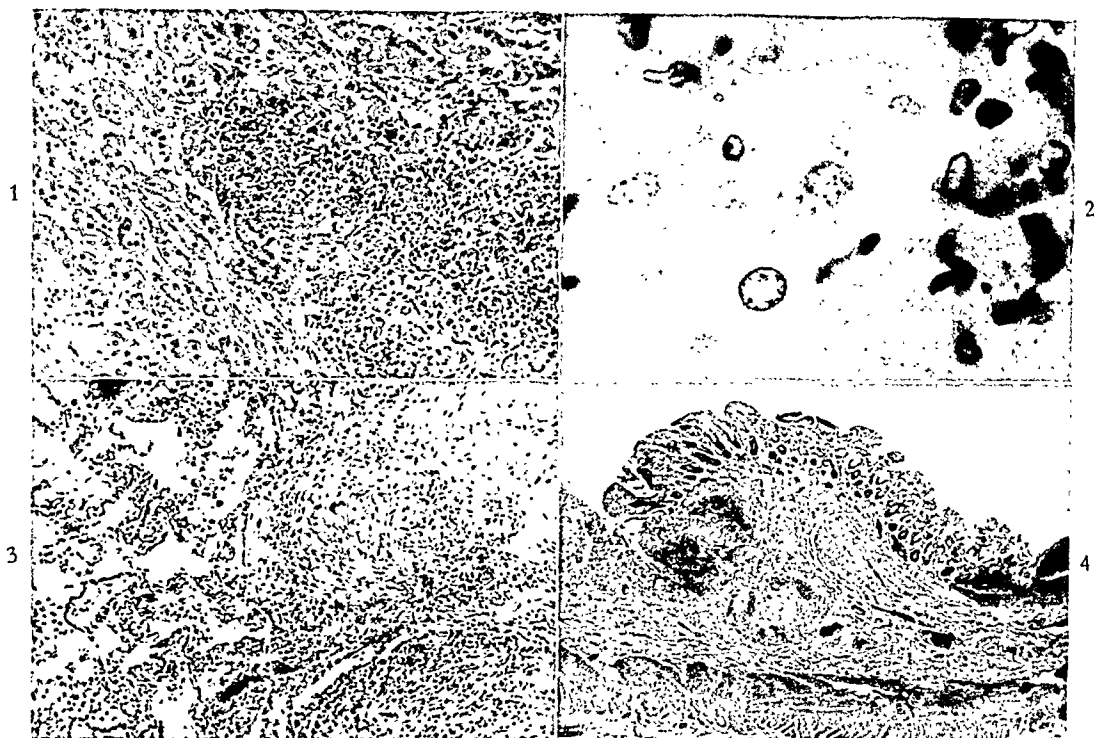


FIG. 1. Section of the adrenal showing a small amount of normal cortex and a granulomatous reaction about a focus of necrosis.

FIG. 2. Oil immersion photomicrograph showing *Histoplasma capsulatum* within macrophages in the adrenal.

FIG. 3. Fibrocaceous tuberculous lesion in the lung.

FIG. 4. Edge of a tuberculous ulcer in the ileum. The base of the ulcer lies to the left of the illustration.

lesion with all the histologic characteristics of tuberculosis. There is a central caseous focus at the right of the photograph which is surrounded by epithelioid cells, lymphocytes, a typical Langerhans giant cell and fibroblasts.

In Figure 4 the margin of an intestinal ulcer is seen; the base lies to the left. The edge of the ulcer is elevated and covers a fibrous and granulomatous lesion in which there is the classical reaction to tuberculosis. Acid-fast organisms were demonstrated in the lesion by the Ziehl-Nielsen stain (Fig. 5); thus it is established that this patient had both tuberculosis and histoplasmosis. Figures 6 and 7 illustrate additional typical tuberculous lesions in the spleen and right seminal vesicle, respectively.

I think that the tuberculous involvement of the seminal vesicle explains the soft tissue mass described in the anterior wall of the rectum. At the time of autopsy the rectum

was examined from the outside, but the region of the mucocutaneous junction was not removed because of consequent technical difficulties in the repair of the body after such a procedure. We did not observe at the time of the autopsy any ulceration at the mucocutaneous junction.

Figure 8 is a section of the thrombus in the pulmonary artery showing that it was considerably organized and had been *in situ* for some time.

In summary, the anatomic findings indicate this patient had chronic tuberculosis involving the lungs, the intestine and the right seminal vesicle with a terminal miliary spread which was of no clinical consequence. This type of terminal spread is often observed in patients with chronic pulmonary tuberculosis and does not represent the disease entity of miliary tuberculosis. In addition there was histoplasmosis limited to the adrenal glands which brought about

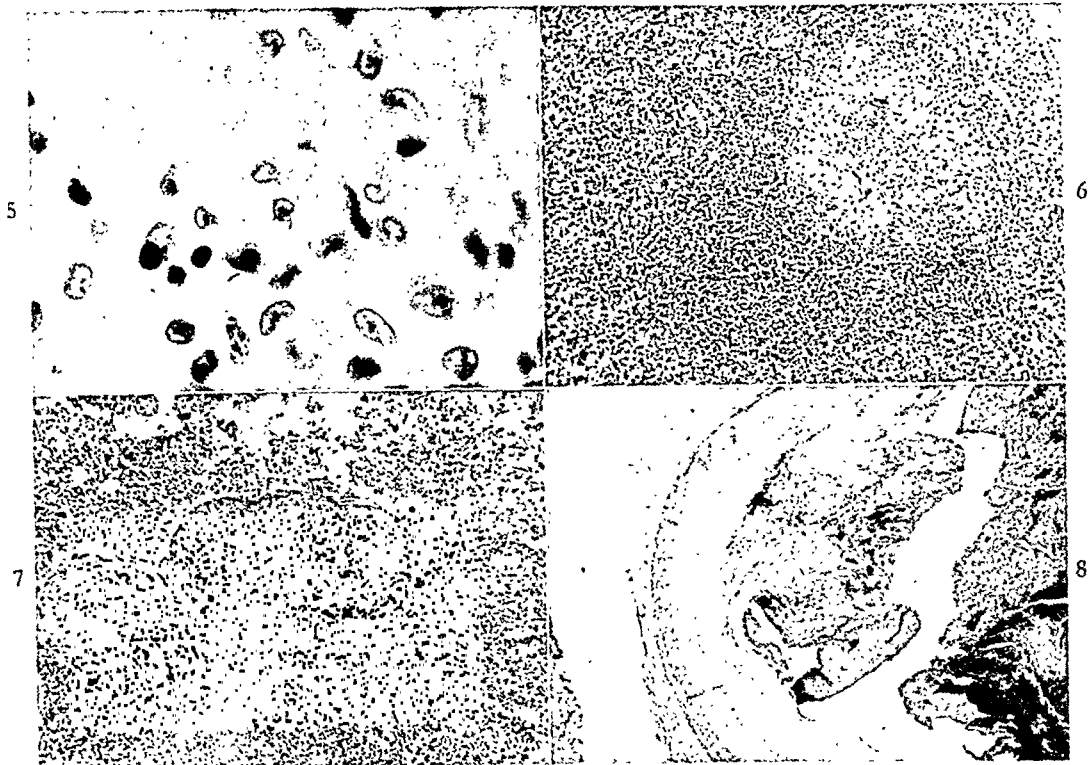


FIG. 5. Rod-shaped, acid-fast organisms in epithelioid cells in the base of the ulcer in the ileum. (Oil immersion lens.)

FIG. 6. Tubercle in the spleen.

FIG. 7. Tuberculous inflammation of the right seminal vesicle.

FIG. 8. Partially organized thrombus attached to the wall of the pulmonary artery in the right lung.

sufficient destruction of the cortices to give the signs and symptoms of adrenal insufficiency.

Final Anatomic Diagnoses: Caseous and fibrocaseous tuberculosis of all lobes of the lungs, especially in the upper lobes, with foci of caseous pneumonia; caseous and fibrocaseous nodules in the tracheobronchial and bronchopulmonary lymph nodes, more marked on the right; fibrosis of the lungs, most advanced in the upper lobe of the right lung; tuberculous ulcers of the ileum and cecum with caseous necrosis of the wall of the ileum; caseous and fibro-

caseous tuberculosis of the serosal surface of the ileum and the adjacent mesenteric lymph nodes; focal granulomas of the liver and spleen; tuberculous seminal vesiculitis, right; histoplasmosis of the adrenal glands, with caseous necrosis (Histoplasma capsulatum cultured from postmortem tissues); partially organized thrombus in a secondary branch of the right pulmonary artery.

Editor's Note: Reprints of these conferences are now available. Requests should be sent to Dr. Robert J. Glaser, Department of Medicine, Barnes Hospital, St. Louis 10, Mo.

Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE EASTERN SECTIONAL MEETING
HELD IN PHILADELPHIA, DECEMBER 4, 1948.

MESENCEPHALOTHALAMOTOMY FOR RELIEF OF INTRACTABLE PAIN. *E. A. Spiegel, M.D. and H. T. Wycis, M.D. (Introduced by L. A. Soloff, M.D.), Philadelphia, Pennsylvania.* (From the Departments of Experimental Neurology and Neurosurgery, Temple University School of Medicine and Hospital.)

A lesion of the long ascending pain-conducting pathways in the mid-brain is combined with a lesion of the dorsomedial nucleus of the thalamus by means of a stereotaxic technic. Since patients become unconcerned about their pain following prefrontal lobotomy and since the dorsomedial nucleus of the thalamus degenerates following this procedure, the lesion of this nucleus is added to that of the long ascending pain-conducting pathways in order to induce a relative indifference to pain perceived through the remaining auxiliary pathways. In a patient suffering from unilateral facial pain for six years, despite retrogasserian rhizotomy, mesencephalothalamotomy on the opposite side abolished the pain completely except for occasional paresthesias in the maxillary region. In a second patient suffering from diffuse burning pain and spasms in the right lower extremity following injury to the lumbar spine and which was unrelieved by sympathectomy, rhizotomy and bilateral chordotomies, bilateral mesencephalothalamotomy reduced the painful area to the region around the right buttock while the spasms of the leg and the sensation of the muscular contractions persisted.

VOLUME CHANGES IN THE FUNCTIONAL DIVISIONS OF TOTAL BODY WATER FOLLOWING THERAPY IN HYPOTHYROIDISM WITH PERICARDIAL EFFUSION. *A. Sokalchuk, M.D., C. T. Bello, M.D. (by invitation), E. M. Greisheimer, M.D. (by invitation), and L. A. Soloff, M.D., Philadelphia, Pennsylvania.* (From the Depart-

ments of Physiology and Medicine, Temple University School of Medicine and Temple University Hospital.)

Recently four consecutive cases of myxedema with so-called "myxedema heart," usually attributed to a uniform dilation of all cardiac chambers, were found to have pericardial effusion on aspiration. With use of the dye T-1824, sodium thiocyanate and percentage change in cellular hemoglobin, estimations were made before and after therapy in three of the aforementioned cases on plasma volume, blood volume, "available fluid space," interstitial fluid volume and percentage change in the intracellular fluid volume. The small number of cases permits only a preliminary report at this time but since the total number of reported cases proven to have pericardial effusion by aspiration has been extremely meager, we believe we are justified in mentioning certain trends.

The plasma and blood volumes are low in these cases and tend to increase under therapy. To date no significant change in interstitial fluid volume has been observed. Changes in plasma volume are reflected in "available fluid space" measurements. Intracellular fluid volume appears to decrease under therapy.

TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE. *J. B. Johnson, M.D., Charles Ireland, M.D. (by invitation), R. F. Thomas, M.D. (by invitation) and Andrew Bass, M.D. (by invitation), Washington, D. C.* (From the Department of Medicine, Howard University Medical School.)

This report presents a study of eleven patients with hyperthyroidism who were treated with I-131. The diagnosis was based on clinical manifestations, basal metabolic rate, blood cholesterol and galactose tolerance test. Five of the patients were previously treated unsuc-

cessfully with other methods, including propylthiouracil, vitamin A or subtotal thyroidectomy. The ages ranged from twenty-two to sixty-three years. The basal metabolic rate during the week preceding therapy ranged from +35 to +90. One dose of I-131 consisting of 0.5 millicuries per estimated Gm. of thyroid was given. The basal metabolic rate and other tests of thyroid function were made at periodic intervals after treatment.

During the first week after therapy the basal metabolic rate fell precipitously in all cases. At the end of ten weeks eight of the eleven patients showed clinical remission, marked reduction in the size of the thyroid, normal basal metabolic rate and associated return of the blood chemical findings toward normal. Another patient required thirteen weeks for a clinical remission. In one patient observations have not been completed. One patient can be classed as unsuccessful. In five of the eleven patients the metabolic rate continued to fall, going below -15. In each of these five subjects the basal metabolic rate spontaneously returned to normal from the hypothyroid level within six to twelve weeks. No serious complications were encountered in any of the patients.

I-131 in adequate dosage is an effective drug in the management of hyperthyroidism. Exact dosage and the duration of remission with I-131 represent problems which are still unsolved.

A METHOD FOR MEASURING COMPARATIVE VELOCITIES OF THE CELLULAR AND FLUID COMPONENTS OF THE BLOOD IN THE PERIPHERAL CIRCULATION. *Edward D. Freis, M.D., Joseph R. Stanton, M.D. and Charles P. Emerson, M.D., Boston, Massachusetts.* (From the Evans Memorial Hospital, Boston University School of Medicine.)

A method is described for measuring the comparative velocities of red cells and plasma in a single circulation through an isolated portion of the peripheral vascular bed in man. With the circulation to the hand occluded, a mixture of plasma labelled with T-1824 and of red cells labelled by means of selective agglutination differences was injected instantaneously into the brachial artery. Simultaneously, and for one and one-half minutes or longer thereafter separate blood specimens were collected every two or five seconds from a large antecubital vein of the same arm. The concentration of the dye

T-1824 and of the donor cells was measured in each specimen and the respective curves of concentration plotted against time. Because of the relatively large concentration of labelled substances injected in respect to the volume of the vascular bed perfused, concentration of the dye and tagged cells removed at the antecubital vein could be measured with considerable accuracy.

Analysis of the time concentration curves so derived indicated that the mean velocity of the red cell mass consistently was greater than that of the plasma mass.

TREATMENT OF PERNICIOUS ANEMIA WITH CRYSTALLINE VITAMIN B₁₂. *Edward H. Reisner, Jr., M.D., (Introduced by Menasch Kalkstein, M.D.), New York, New York.*

Vitamin B₁₂, a crystalline cobalt complex isolated from liver, has been found to have tremendously high antipernicious anemia activity. It is believed to be the actual anti-anemic principle of liver. West and Reisner treated eleven patients with pernicious anemia in relapse with varying doses of B₁₂. Maximal reticulocyte responses were obtained from a single injection of as little as 6 gammas. The potency of the material as determined by these studies is slightly more than 1 international unit per gamma. Of the eleven patients five had combined system disease. The early cord lesions were completely relieved and later manifestations vastly improved by B₁₂ therapy. Vitamin B₁₂ sufficed to bring about full remission of the blood count in patients maintained on it. It is not known yet what the relationship is between B₁₂, pteroylglutamic acid and thymidine.

TREATMENT OF PRIMARY ATYPICAL NON-BACTERIAL PNEUMONIA WITH AUREOMYCIN. *Emanuel B. Schoenbach, M.D. and Morton S. Bryer, M.D., Baltimore, Maryland.* (From the Department of Preventive Medicine, Johns Hopkins University School of Medicine.)

Primary atypical non-bacterial pneumonia has been extensively investigated during the past seven years and no therapeutic agent has been found to influence the course of the disease. Ten patients with primary atypical non-bacterial pneumonia have been treated with oral aureomycin, a new antibiotic derived from cultures

of *Streptomyces aureofaciens*. These patients were ten to fifty-nine years of age and had been ill for one to nine days before aureomycin therapy was instituted. The diagnosis was established by history of non-productive cough, fever, headache, chills, positive x-ray evidence of pulmonary consolidation, relative leukopenia, essentially negative bacteriologic examination and by serologic studies. The latter included tests for the presence of cold agglutinins, agglutinins for the streptococcus MG, antibodies for Q fever, influenza and the psittacosis group on serial bleedings.

The patients treated with aureomycin became afebrile within twenty-four to seventy-two hours. Most patients were afebrile in less than forty-eight hours. In only one patient, with extensive involvement of four lobes, the temperature fell precipitously but did not become normal until seventy-two hours after institution of aureomycin therapy. The clinical response of these patients paralleled the rapid defervescence of fever. Convalescence was uneventful except for mild transitory thrombophlebitis in one patient and probable thrombosis and leukocytosis several days after the drug had been stopped in another. Both these patients had developed high titers of cold agglutinins during this period.

The drug was well tolerated and no toxic or untoward reactions were noted. The total amount of drug administered varied from 3.8 to 8.0 Gm. over a five to seven-day period. Aureomycin has not been noted to have an antipyretic effect in many other infections.

These results indicate that aureomycin may be a valuable therapeutic agent for the treatment of primary atypical non-bacterial pneumonia.

TUBERCULOUS PERITONITIS TREATED WITH STREPTOMYCIN. *Thomas McP. Brown, M.D. and Ruth H. Wichelhausen, M.D. (introduced by Joseph F. Sadusk, Jr., M.D.), Washington, D. C. (From the Medical Department, Veterans Administration Hospital.)*

Two patients with tuberculous peritonitis were treated with streptomycin and the clinical records of twenty-four additional patients treated in various Veterans Administration Hospitals were reviewed by the authors. Duration of treatment varied between 25 and 164 days; total dosage of streptomycin was between 43 and

349 gm. Response to treatment was manifested chiefly by subsidence of fever and ascites, amelioration of abdominal symptoms, a feeling of general well being and gain of weight. The peritoneal involvement responded favorably in twenty-four of twenty-six cases regardless of duration of symptoms prior to therapy. Several patients developed new tuberculous lesions elsewhere during or after streptomycin therapy but recovered clinically from the peritonitis.

Twenty-two of twenty-six patients had no significant abdominal symptoms after cessation of therapy. Two patients relapsed and responded to a second course of streptomycin. There were two deaths, one patient with pulmonary and peritoneal involvement failed to show definite response to therapy and the other showed temporary improvement with relapse and subsequent death when the drug was discontinued because of toxicity. In six of the patients who received less than 80 Gm. of streptomycin two deaths and one relapse were observed. There were no deaths and one relapse in the remaining twenty patients who received 86 Gm. or more of streptomycin. Follow-up observations have been possible in nineteen patients, ten have been followed for six to eighteen months and nine for less than six months.

Three patients were re-explored electively shortly after cessation of therapy and striking improvement was demonstrated. All three have remained clinically well for six to twelve months. Two biopsy reports are available. One patient showed no microscopic evidence of tuberculosis. The histologic diagnosis in the other was tuberculosis of the peritoneum.

The interpretation of the final results of streptomycin therapy in tuberculous peritonitis must await prolonged observation.

BCG VACCINATION IN SARCOIDOSIS. *Harold L. Israel, M.D., Maurice Sones, M.D. and Samuel C. Stein, M.D., Philadelphia, Pennsylvania. (From the Woman's Medical College of Pennsylvania and The Henry Phipps Institute of the University of Pennsylvania.)*

Since the relationship between sarcoidosis and tuberculosis remains questionable, an attempt was made to ascertain the response of patients with sarcoidosis to artificial inoculation with living, avirulent tubercle bacilli. Intracutaneous BCG vaccination has been per-

formed with cultures and technic that produces conversion to positive tuberculin reaction in 93 per cent of normal persons.

Eighteen patients with sarcoidosis have been vaccinated with BCG. Three of these patients early in the study had strong clinical and laboratory evidence to support the diagnosis but biopsy material was not available. More recently vaccination has been restricted to patients with typical histologic lesions. In many cases guinea pig inoculation of the material has been performed. Two patients have been vaccinated twice. Sixteen patients have been under observation for three months or more and have had tuberculin tests after vaccination. None became positive to first strength PPD, nine became positive to second strength PPD, three had doubtfully positive reactions to second strength PPD and four had negative reactions. Of the nine who had positive reactions five have subsequently changed to negative.

Preliminary results indicate an inability on the part of sarcoid patients to develop and maintain tuberculin allergy. Study is now in progress to determine whether this immunologic defect is specific or general.

SERUM COMPLEMENT IN RHEUMATIC FEVER AND OTHER CONDITIONS. *Edward E. Fischel, M.D., New York, New York.* (From the Department of Medicine, Columbia University College of Physicians and Surgeons and the Edward Daniels Faulkner Arthritis Clinic of The Presbyterian Hospital.)

Quantitative serial studies were made of total serum complement (C') in normal subjects and in various pathologic conditions, using the spectrophotometric technic for determination of the 50 per cent hemolytic unit with optimal concentrations of magnesium and calcium according to Heidelberger and co-workers. Repeat determinations gave values of ± 1.1 units.

The C' content of a series of normal sera was 37.6 ± 3.9 units per ml. Low C' levels (11–20 units) were found in certain allergic states such as serum sickness and also in acute glomerulonephritis. Gradual restitution of C' occurred with recovery. High C' levels (51 to 89 units) were found in some drug allergies, in thirty-one of thirty-three cases of rheumatic fever followed serially and in other febrile illnesses. Only two

patients with rheumatic fever were found with a low C' which gradually became normal. The elevated C' in rheumatic fever appears to be a sensitive criterion of activity of the rheumatic process. Occasionally recrudescences were seen with an initially normal sedimentation rate and an elevated C' .

The low complement level in serum sickness may be due to fixation of C' by an antigen-antibody complex. However, low levels in this and other conditions may be due to other causes, such as an increase in gamma globulin and other anticomplementary substances or a diminished production of complement.

REDUCTION IN CIRCULATING EOSINOPHILS FOLLOWING EPINEPHRINE, INSULIN AND SURGICAL OPERATIONS. *Thomas P. Almy, M.D. and John H. Laragh, M.D. (by invitation), New York, New York.*

Reduction of the absolute number of circulating eosinophils following pituitary adrenocorticotrophic hormone (ACTH) has been shown to depend upon the presence of normally functioning adrenal cortices. The adrenal cortex of animals is known to be stimulated by epinephrine, by insulin and by non-specific stress.

In the present work twenty healthy persons given 0.5 cc. of 1:1,000 epinephrine subcutaneously responded with a fall in circulating eosinophils within three hours, averaging 56 per cent of the initial count. In twelve subjects given intravenous insulin (0.1 unit 1 Kg.) the eosinophil count fell an average of 57.5 per cent in four hours. Profound eosinopenia was noted three to eight hours following surgical operations in fourteen of fifteen subjects, the average drop being 85 per cent.

The response to epinephrine or insulin was diminished or absent (average fall 6.8 per cent) in four subjects with adrenal insufficiency and in two patients with hypopituitarism. The response was normal (average fall 55.2 per cent) in six patients with pituitary tumors in which hypopituitarism was absent. The response was exaggerated (average fall 82 per cent) in five patients with essential hypertension.

THE NATURE OF THE COAGULATION DEFECT IN HEMOPHILIA: STUDIES ON PLATELET-FREE PLASMAS. *Robert C. Hartman, M.D., C. Lockard Conley, M.D. and John S. Lalley, M.D. (introduced by George S.*

Mirick, M.D.), Baltimore, Maryland. (From the Division of Clinical Microscopy, Department of Medicine, Johns Hopkins University and Hospital.)

By means of silicone-treated apparatus and high speed centrifugation at low temperatures, platelet-free plasma can be prepared without the use of anticoagulants. This plasma remains fluid at 2°C. for at least several days. Invariably normal platelet-free plasmas clot in a relatively short time when transferred to glass tubes at 37°C., but in silicone-treated tubes the clotting time is greatly prolonged and with perfect technic no clotting at all may occur. On the other hand, hemophilic platelet-free plasmas are spontaneously incoagulable in both glass and silicone-treated tubes at 37°C. No evidence was found for the existence of a clotting inhibitor in the plasmas from the uncomplicated cases of hemophilia studied. The authors concluded that in normal plasma an inactive thromboplastin exists which can be activated by contact with surfaces which can become wet. This factor is apparently deficient in hemophilic plasma. This inactive plasma thromboplastin shows the same physiologic activity and may be identical with the antihemophilic globulin of Patek and Stetson.

THE CLOTTING MECHANISM IN LIVER DISEASE: A PRELIMINARY REPORT. *W. J. Harrington, M.D., C. Crow, M.D., H. Minkel, M.D., J. Desforges, M.D. (by invitation) and R. Manheimer, M.D. (by invitation), Boston, Massachusetts. (From the 1st and 3rd Medical Services (Tufts) Boston City Hospital.)*

It has been observed that in diffuse liver disease a tendency to abnormal bleeding occurs, often unassociated with significant alteration of the prothrombin clotting time. Nor has the clotting time (C.T.) in glass consistently revealed any coagulation defect. This is a report on the investigation of sixty-five patients; studies included clotting times in glass and in silicone-coated tubes and one-stage prothrombin clotting times.

In thirty cases of Laennec cirrhosis twenty-two patients showed prolonged C. T. in silicone while only one was prolonged in glass. In two cases of toxic cirrhosis normal C. T. were found and this was true of two cases of cholangiolitic

hepatitis. In fifteen cases of infectious hepatitis all clotting times were prolonged in silicone and four were prolonged in glass. In four cases of acute obstructive jaundice there were two slightly prolonged C. T. in silicone and none in glass. Of seven cases of chronic obstructive jaundice all had prolonged clotting time in silicone and five were prolonged in glass. In five cases of metastatic cancer to the liver one patient showed a slightly prolonged C. T. in silicone.

There was no relationship between the prolonged clotting time in silicone and the prothrombin clotting time unless prothrombin clotting time was below 30 per cent of normal. In this instance, except in two cases, all the clotting tests in silicone were prolonged.

EVIDENCE THAT DYES USED IN TESTING LIVER FUNCTION ARE REMOVED BY HEPATIC PARENCHYMAL CELLS RATHER THAN BY KUPFFER CELLS. *Albert L. Mendeloff, M.D. (introduced by Kendall Emerson, Jr., M.D., Boston, Massachusetts. (From the Evans Memorial, Massachusetts Hospitals and the Department of Medicine, Boston University School of Medicine.)*

Although certain intravenously administered dyes have been used in the assessment of hepatic function for years, the exact mechanisms by which the liver removes them from the blood are poorly understood. The relative importance of the hepatic parenchymal cells and the Kupffer cells in the removal of the dyes has not yet been ascertained.

The dye rose bengal (tetrachlor-tetraiodo-fluorescein), was found to emit an orange-brown fluorescence in ultraviolet light of wavelengths 3150 to 3650 Ångströms. Tissues stained with 1 to 2 per cent solutions of this dye emitted strong fluorescence which was readily observed by long ultraviolet light through glass condensers, mirror and slides.

Aqueous solutions of the dye (1 to 2 per cent) were administered intravenously to twenty rabbits; liver and splenic biopsies were taken from one to fifteen minutes thereafter. The tissues were immediately frozen and cut in 15 micra sections, floated on water and mounted. The characteristic sustained fluorescence of rose bengal was noted constantly in the hepatic parenchymal cells; no such fluorescence was seen in the Kupffer cells which emitted their

characteristic yellow-green, rapidly fading fluorescence. The fluorescence due to rose bengal was absent or very faint in splenic tissue and apparently when present was located in the sinusoids rather than in the parenchyma.

Since other evidence obtained in this laboratory, in man, shows that the hepatic uptake of rose bengal is slowed or blocked by simultaneously-administered bromsulfalein, it is suggested that normal removal of these dyes from the blood stream is a function of the hepatic parenchymal cells rather than of the Kupffer cells.

DIAGNOSIS OF CARCINOMA OF THE BILIARY TRACT AND PANCREAS BY SMEARS OF EXFOLIATED CELLS IN DUODENAL DRAINAGE. *W. W. Byrnes, M.D., H. M. Lemon, M.D. and G. F. Miller, M.D., (introduced by Kendall Emerson, Jr., M.D.), Boston, Massachusetts.*

The cytology of the duodenal drainage in a series of over thirty-five diagnostic problems has been investigated with a modification of Papanicolaou's method for staining exfoliated cells. The technic of Lyons has been used in the drainage. The series includes twelve patients with carcinoma of the liver, extrahepatic biliary tract, pancreas and stomach, most of which have been verified pathologically. In this small series 90 per cent accuracy has been achieved in providing histologic indications for surgical intervention in cases of cancer of the bile ducts and pancreas. There has been a very good correlation between tumor cytology and the suspected malignant cell clumps in duodenal drainage. It is believed that this method will provide a means of earlier diagnosis of primary and secondary cancers of the liver, bile ducts, ampulla of Vater, and pancreas since even tumors less than 2 cm. in diameter have yielded highly characteristic cytology.

DIAGNOSTIC VALUE OF DIFFERENTIATING BETWEEN MORPHOLOGICALLY IDENTICAL CELLS BY TISSUE CULTURE. *Machteld E. Sano, M.D. and Carmen T. Bello, M.D., Philadelphia, Pennsylvania.* (From the Department of Research Pathology and the Department of Internal Medicine, Temple University Hospital and Medical School.)

The histopathologic study of pleural effusions and lymph nodes is frequently disappointing.

This is especially true in cases in which the clinical diagnosis is obscure and in which cytologic study is the last hope for obtaining a clear cut diagnosis. In the last ten years the study of lymph nodes by tissue culture has shown that cells originating from tissues with similar histopathology and morphology may grow quite differently. The study of pleural effusions also has shown that cells which appear morphologically identical behave differently in a tissue culture. This is especially true of idiopathic effusions of which we present three cases to illustrate our point.

The history of the first patient and the clinical picture suggested metastatic tumor. X-ray of the spine also suggested multiple metastases. Histopathology revealed lymphocytes, monocytes and occasional neutrophils. On tissue culture there was rapid development of giant cells with a granular center and multiple nuclei. There were epithelioid cells and lymphocytes. A diagnosis of tuberculosis was made. The patient died of meningitis and a positive culture of Koch bacilli was obtained from the spinal fluid.

The second case, a sixty-five year old woman, presented fluctuating temperature and pain in the right side of the chest. Cytologic study of the pleural effusion was not revealing. Tissue culture showed rapidly developing cells with bi- and trilobed nuclei. The small lymphocytes showed numerous mitoses. A diagnosis of malignant lymphoma was made, probably a reticulum cell sarcoma with some of the characteristics of a lymphosarcoma. This was confirmed at a later date by biopsy of a lymph node.

In the third case the tentative clinical diagnosis was lung tumor. In tissue culture the lymphocytes, monocytes and occasional neutrophils showed very little activity and rapidly disintegrated. This behavior suggested a regressive process. The patient after thoracentesis recovered rapidly and has been well these last six months.

THE DIAGNOSIS OF ANGINA PECTORIS—A NEW APPROACH. *Herbert R. Brown, Jr., M.D. and Marvin J. Hoffman, M.D. (by invitation), Rochester, New York.* (From the Department of Medicine, University of Rochester School of Medicine and Dentistry and Medical Clinic of The Strong Memorial and Rochester Municipal Hospitals.)

The atypical case of angina pectoris is often missed or confused because of the lack of objective diagnostic criteria. A new approach to more accurate diagnosis correlates elements of history, physical findings, the electrocardiogram when positive and the ballistocardiogram.

The patients were divided as follows into four groups based upon symptomatology: (1) typical cases of angina pectoris without a history of coronary failure or coronary occlusion, (2) typical cases of angina pectoris with a history of coronary failure, (3) coronary thrombosis with myocardial infarction and (4) the atypical cases in which ascertaining the presence or absence of coronary artery disease is at present done with considerable uncertainty.

The most significant positive factor in this series was the establishment of a correlation between the definite cases of angina pectoris and abnormal ballistocardiographic tracings. The first ballistocardiographic evidence of abnormality is an increased respiratory variation brought about by a decreased amplitude during expiration. This probably results from a decreased venous return. Further abnormalities are indicated by the presence of irregularity, lack of definition and decreased amplitude throughout all of the wave patterns. The cases of coronary failure and myocardial infarction revealed through the ballistocardiogram a more severe degree of impairment. This relationship was next used to detect the presence or absence of coronary artery disease in atypical cases. This approach represents a means of diagnosing angina pectoris, typical or atypical, with a consistency heretofore unobtainable.

EFFECT OF EPINEPHRINE, AMINOPHYLLINE AND DIGITOXIN ON THE OXYGEN CONSUMPTION OF RABBIT HEART SLICES.
Leon Levinson, M.D. and Mark Aisner, M.D., Boston, Massachusetts. (From the Departments of Physiology and Medicine, Tufts College Medical School.)

Vasopressor substances have generally been regarded as contraindicated in the shock-like state following myocardial infarction. Such substances are believed to cause an increase in the oxygen consumption of the myocardium proportionally greater than the accompanying increase in contractile force, and thus to endanger the tissue in the hypoxic border of the infarct. Digitalis is also generally withheld from

patients with recent myocardial infarcts for similar reasons. Aminophylline, on the other hand, is often given freely although evidence has been presented indicating that this drug may also increase the work of the heart.

Slices of rabbit heart were suspended in a glucose-containing modified phosphate-buffered Ringer's solution and oxygen consumption determined by the Warburg technic. No statistically significant effect upon oxygen consumption occurred when epinephrine (1 by 10^{-5} and 1 by 10^{-7}), digitoxin (2 by 10^{-5} and 2 by 10^{-7}) or aminophylline (1 by 10^{-4}) was added. The lower concentrations employed approximate clinical dosage.

The oxidative metabolic mechanism of non-contracting heart muscle is thus unaffected by these drugs. These substances, however, have definite effects on the metabolism of contracting muscle as measured in the Gold papillary muscle preparation. In the dog ligation of a coronary artery leads to immediate cessation of contraction of the involved area. So far as non-contracting tissue is concerned administration of epinephrine, aminophylline or digitoxin has no apparent effect.

MYOCARDIAL LACTATE AND PYRUVATE METABOLISM STUDIED IN NORMAL AND HYPERGLYCEMIC INTACT DOGS BY CORONARY SINUS CATHETERIZATION. *Walter T. Goodale, M.D., Donald B. Hackel, M.D., Martin Lubin, M.D. and Pauline P. Wilson, M.D. (introduced by Kendall Emerson, Jr., M.D.), Edgewood Arsenal, Maryland.* (From the Medical Division, Army Chemical Center.)

Preferential utilization of lactate and pyruvate by heart muscle has been demonstrated but never under normal physiologic conditions. Development of a technic of catheterizing the coronary sinus under fluoroscopic control, however, has made it possible to study myocardial metabolism in both nembutalized and unanesthetized intact dogs.

Coronary arteriovenous differences were estimated from blood samples drawn simultaneously from femoral artery and coronary sinus. Coronary blood flows were measured by the nitrous oxide method. Total myocardial utilization was the product of two independent variables: (1) coronary blood flow and (2) coronary arteriovenous difference. In normals,

coronary arteriovenous lactate and pyruvate differences were, in turn, closely and directly correlated with the respective arterial blood levels.

The mean myocardial lactate utilization was 7.5 mg. per 100 Gm. of heart muscle per minute, and pyruvate utilization was 1.1 mg., with a mean myocardial oxygen consumption of 12 cc./100 Gm./min. Assuming complete oxidation of lactate and pyruvate in the heart, the amounts removed could together account for anything up to 80 per cent of the current myocardial oxygen consumption, this percentage depending in the normal almost entirely upon the arterial levels of each metabolite. No myocardial glucose utilization was demonstrable and no ketone body utilization was found at normal levels. In hyperglycemia from glucose infusion, lactate and pyruvate blood levels rose but with the same myocardial lactate and pyruvate utilization compared to their arterial levels as was found in normals.

Lactate and pyruvate thus appear to be preferred sources of energy for the myocardium and are increasingly utilized as their arterial levels and the coronary blood flow rise. Glucose, even when present in excess, apparently does not compete with lactate or pyruvate for myocardial utilization. These facts may help to explain logically the excellent adaptation of the heart to stress or to the increased work of severe exercise.

ELECTROLYTE CHANGES IN CONGESTIVE HEART FAILURE: EFFECTS OF ADMINISTRATION OF POTASSIUM AND SODIUM SALTS. Charles L. Fox, Jr., M.D., Charles K. Friedberg, M.D. and Abraham G. White, M.D. (by invitation), New York, New York. (From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University and the Medical Service, Mt. Sinai Hospital.)

The electrolyte pattern of the plasma, edema fluid and urine during acute congestive heart failure and after recovery was investigated together with the effects of administering various mixtures of potassium and sodium salts.

With chronic congestive heart failure, the plasma sodium was subnormal (112 to 132 mEq. per L.) in nineteen patients; two patients had high values (148 and 150); five patients ranged from 133 to 142. Plasma chlorides did not

parallel sodium; they were reduced in nine patients (93 to 101 mEq. per L.) and elevated in twelve patients (106 to 112 mEq. per L.) with four in the normal range (101 to 106 mEq. per L.). Plasma potassium was subnormal in ten (2.3 to 3.5), above normal in three (5.4, 5.8 and 7.3) and normal (4 to 5) in six. After recovery from failure measurements were repeated in five patients and plasma sodium increased from 4 to 15 mEq.; plasma potassium when subnormal also increased (3.0 and 3.2 going to 5.0 and 5.2, respectively).

After injection of a mercurial diuretic but before the onset of diuresis, changes in the electrolyte composition of the edema fluid were observed. With diuresis, marked changes in the electrolyte pattern of the urine resulted. The administration of NaCl or KCl resulted in positive chloride balances and weight gain. When these cations were given with organic anions, little or no weight gain occurred despite the markedly positive sodium balance. Simultaneous administration of K acetate and NaCl diminished the weight gain and positive chloride balance.

In these studies gain or loss of weight did not appear to be a simple function of sodium balance. The observations suggest that intracellular and extracellular ionic relationships may play a part in the phenomena of congestive heart failure.

LIFE SITUATIONS, EMOTIONS AND HUMAN COLONIC FUNCTION. William J. Grace, M.D., Stewart Wolf, M.D. and Harold G. Wolff, M.D. (by invitation), New York, New York. (From the Departments of Medicine and Psychiatry of the New York Hospital and Cornell University Medical College.)

We have had a unique opportunity to study the behavior of the human colon in two fistulous subjects, with particular emphasis on the influence of emotions and feeling states. Subject A had a large prolapse of the ascending colon and cecum through a cecostomy wound. Subject B had a large prolapse of the descending colon and sigmoid through a colostomy incision.

Our findings indicate that situations productive of anger, guilt, resentment and hostility are accompanied by hyperfunction of the large bowel. This hyperfunction is manifested by an increase in motor activity, blood flow,

lysozyme production and usually mucus secretion. In severe induced pain under experimental circumstances there was intense fear and fright and a pallor and relaxation of the large intestine. Increase in motor activity, blood flow and secretion of the large bowel occurred regularly following ingestion of an average meal. However, in one of our subjects little change in activity was noted when he was in a period of low spirits, dejection and mild depression. Other threats to bodily and personal integrity, such as sigmoidoscopic examination, personality study and having the patient perform a psychometric test, resulted in an increase in motor activity and blood flow. A period of sustained anger, resentment and hostility resulted in a profuse eruption of petechiae throughout the surface of the exposed colon.

COMPARATIVE STUDY OF THE EFFECTS OF MILK AND HYDROLYZED PROTEIN ON GASTRIC AND DUODENAL BULB ACTIVITY IN DUODENAL ULCER. *Mieczyslaw S. Lopusniak, M.D. (introduced by Irwin J. Pincus, M.D.), Philadelphia, Pennsylvania.* (From the Graduate Hospital of the University of Pennsylvania.)

The studies on which this report are based were undertaken: (1) to observe the effects of an aqueous mixture of casein hydrolysate, dextrans and maltose on the acidity of the contents of both the duodenal bulb and pars pylorica in patients with active duodenal ulcer and (2) to compare these effects with those of milk and a mixture of milk and cream. Eleven patients with clinical and roentgenologic evidence of active duodenal ulcer were selected for study. The amount of each foodstuff and the frequency of administration were so chosen as to duplicate clinical methods of treating ulcers which utilize these substances. Material was extracted by means of a special double-lumen tube from either side of the pylorus before and at intervals after the feeding of each of the substances under investigation.

It was found that casein hydrolysate more effectively buffered and neutralized gastric and duodenal bulb acidity over a two-hour period than did an equal quantity of milk or a mixture

of milk and cream fed hourly over the same period. Under the experimental circumstances of the study and on the basis of the criteria used the hydrolyzed protein mixture employed was, nevertheless, an imperfect buffer and neutralizer of gastric and duodenal bulb acidity in these duodenal ulcer patients. Fairly marked secondary stimulation of active secretion in the stomach regularly followed its ingestion.

STUDIES IN PULMONARY FUNCTION BEFORE AND AFTER PULMONARY RESECTION FOR BRONCHIECTASIS AND OTHER PULMONARY DISEASE. *Joan H. Long, M.D., W. Emory Burnett, M.D., Charles M. Norris, M.D. and M. R. Wester, M.S. (introduced by Thomas M. Durant, M.D.), Philadelphia, Pennsylvania.*

By means of external spirometry and bronchspirometry, changes in the volume of air moved and in oxygen absorption after the surgical removal of one or more pulmonary segments have been studied in sixty-four patients with bronchiectasis and in five patients with other pulmonary disease. Studies were done pre-operatively two weeks postoperatively and again six months to two years later.

It was found that in unilateral bronchiectasis the oxygen absorption is reduced more than the volume of air moved on the affected side. The maximum breathing capacity during voluntary effort is reduced in a manner roughly proportional to the extent of the disease. This decrease is due in most instances to a decrease in the depth of respiration during this effort. After the resection of one or more pulmonary segments the voluntary maximum breathing capacity may be increased.

Only occasionally is there an increase in the percentage of the total air moved by the remaining lung segment on the operated side; usually there is no change or a decrease of the percentage of air moved by that side. On the other hand, it is a little more common to find an increase in the percentage of the total oxygen absorbed by the remaining lung segment on the operated side although, again, in the majority of cases there is either no change or a decrease in this function.

Case Reports

Fulminating Fatal Gout*

H. SPITZ, M.D., O. STEINBROCKER, M.D. S. SCHWARTZ and M. SCHITTONE, M.D.

New York, New York

RECENT reports¹⁻³ have tried to focus the interest of the medical practitioner on articular gout again since it is all too often neglected in the differential diagnosis of acute and chronic joint diseases. Gout is much more common than is generally suspected. Although it is apt to become a chronic disease, severe disabling changes are rare. The comparatively few reports of cases in which extensive crippling deformities developed with ankylosis and marked limitation of motion invariably describe a long protracted course of the disease.³⁻¹⁰ Rapid progression of the disease to a crippling stage in the course of only three years is therefore unusual, particularly when the first symptoms do not appear until the fifth decade of life. Such a case was observed with postmortem examination on the wards of Bellevue Hospital and is herewith reported. Another remarkable feature in this case was the association of severe gout with anemia, splenomegaly and sclerosis of the portal vein.

Occasional case reports have appeared describing gout accompanied by various blood dyscrasias such as pernicious anemia,^{11,12} hemolytic jaundice,^{10,13,14} erythronoclastic anemia¹⁵ and anemia of undetermined type.¹⁶ In several instances splenomegaly with anemia are described without further remarks about the type of the anemia.^{6,17,18} No mention, however, is made in these reports of the appearance of the portal vein. Therefore, it seems that this is the first reported case showing sclerosis and calcification of the portal vein and its main tributaries associated with "splenic anemia" and gout.

CASE REPORT

C. L., a forty-seven year old, unmarried Chinese male who worked as a waiter, was admitted to the hospital on September 12, 1944, with chief complaints of pain in all his limbs (knees, feet, wrists, hands and elbows). He had felt well until three years before when he experienced a sudden pain in his big right toe followed by pain in his legs and arms. Simultaneously, small lumps appeared on his hands and about his joints. The lumps enlarged progressively, became more numerous and were tender to pressure. Pain in his extremities gradually became more severe. For the two years before admission he was unable to work. The pain was lancinating and almost continuous just before admission. Anorexia had been present for two months, with resulting marked weight loss. He had difficulty in retaining urine; the systemic review was otherwise negative.

Examination on admission revealed a cachectic, restless Chinese in acute pain. His temperature was 100°F., pulse 80, respiration 30 and blood pressure 146/76. The head, eyes, ears, nose, throat and lungs were normal. His heart was greatly enlarged to the left. Over the precordium a loud, blowing, systolic murmur was heard. The rhythm was regular. The liver edge was said by some examiners to be sharp and 2 cm. below the right costal margin. The lower pole of the spleen was found to be about 8 cm. below the left costal margin, smooth, non-tender and ballotable because of the presence of peritoneal fluid. There was no abdominal tenderness or rigidity. The kidneys were not felt. The prostate was hard, nodular and slightly enlarged.

There was hyperkeratinization of the skin, most noticeable over the waistline, legs and feet, with ulceration, crusting and painful edema of the feet, particularly of the dorsal surfaces. Numerous freely movable, subcutaneous nodules were felt in the thighs, around the elbows and

* From the Laboratory of Pathology and the Fourth Medical Division (N.Y.U.), Bellevue Hospital, New York, N. Y.

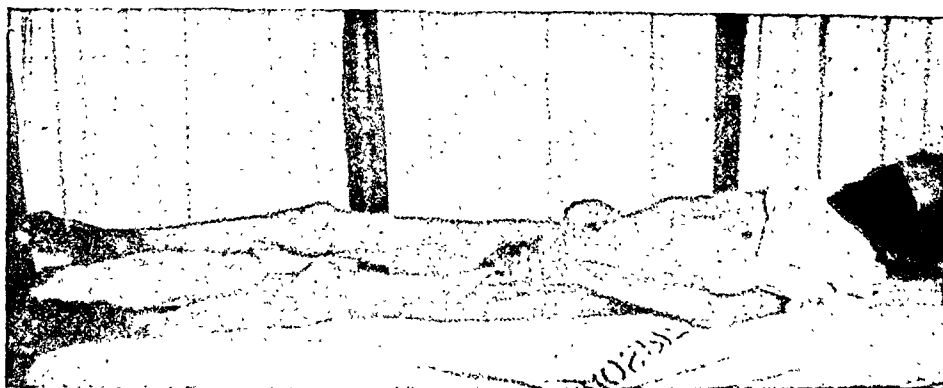


FIG. 1. Nodules over the knees and hands; cachexia.



FIG. 2. X-ray of the right hand. There are no definite punctate erosions despite destructive changes in the middle phalanx of the middle finger where a subcutaneous and an osseous tophus were present with fistula formation. The lesion in the fifth metacarpal bone was interpreted as chondroma.

knees and along the fingers. (Fig. 1.) All of these were tender and in addition some were fluctuant. The hard nodules had a yellowish tint and the veins nearby were distended and surrounded with small hemorrhages. One of the nodules on the right middle finger had broken

down and was discharging cheesy, gritty material containing needle-like crystals. The extremities were wasted and had flexion deformities.

Laboratory data on admission revealed a white blood count of 10,000 with 82 per cent polymorphonuclears and 18 per cent lymphocytes; red blood cells, 1.7 million and hemoglobin 4.5 Gm. Blood Wassermann and Kahn tests were negative. The urine was acid, its specific gravity was 1.014. It contained no albumin, glucose or pathologic microscopic sediment. The blood non-protein nitrogen was 31 mg per cent; uric acid on whole blood, 7.7 mg. per cent; serum calcium 9.1 mg. per cent; phosphorus 3.9 mg. per cent. The cephalin flocculation test was strongly positive; albumin globulin ratio 3.1/4.5; alkaline phosphatase 21.1 Bodansky units; total cholesterol 105 mg. per cent and esters 49 mg. per cent.

The icteric index was 5 on September 13th and rose to 18 on September 20th when a direct, immediate Van den Bergh reaction was obtained. Stool examination for parasites was negative. The electrocardiogram did not reveal any abnormality. X-ray of the chest showed a moderate increase in the size of the heart, with diffuse engorgement in both lungs. In both knee joints hypertrophic changes were found. An expansion of the shaft of the fifth metacarpal bone was interpreted as chondroma. (Fig. 2.) The proximal phalanx of the third right finger showed evidence of periostitis. (Fig. 2.) There was periarticular soft tissue swelling of the right ankle joint. Osteo-arthritic changes were noted in the tarsal bones.

The patient ran an irregular febrile course with occasional rises of temperature to 103°F. On the seventh hospital day a transfusion of 500 cc. of whole blood was given without incident. Immediately following this procedure the temperature dropped to normal and remained

so. The patient was treated with full doses of colchicine and aspirin and with large amounts of multiple vitamins and iron without subjective or objective improvement. His condition deteriorated rapidly until his death on the twenty-seventh hospital day.

Autopsy was performed eight days after death. It revealed an emaciated Chinese male of slender body build appearing somewhat older than the stated age of forty-seven. There was no peripheral edema. No icterus of the sclerae was noted. The superficial lymph nodes were not enlarged. The skin was dry, inelastic and scaly. The feet and hands were covered with numerous subcutaneous nodules varying in diameter from 0.5 to over 3 cm. The nodules were most numerous over the extensor and flexor surfaces of the metacarpophalangeal joints. They were present to a lesser extent over the shafts of the phalanges, metacarpal bones, wrist, elbow, ankle and knee joints. Nodules also were present along the long bones of the upper and lower extremities. No tophi were found in the earlobes. Many of the nodules were attached to the underlying structures but not to the skin. Some were soft and fluctuant while others were firm. One nodule on the dorsal aspect of the right middle finger had ulcerated through the skin and white chalk-like, gritty material could be expressed. Smears of this material showed characteristic sheaves of doubly refractive urate crystals. The ankles and dorsal aspects of the feet were slightly swollen. The overlying skin was superficially excoriated and stained violet (gentian violet). The joints of the fingers and toes showed marked decrease of passive mobility although rigor mortis had completely subsided. Bony hard excrescences were felt along the joint lines of the knees, elbows and wrists. An incision over the dorsum of the left hand exposed numerous tophi on the extensor and flexor surfaces of the hand. The nodules involved tendon sheaths and ligaments and widely replaced the muscles of the palm. Some of the nodules were composed of opaque, gritty material and others contained pale green pus. The first metacarpophalangeal joint was opened. The exposed cartilage was smooth of surface but thinner than normal, opaque and chalky white. Longitudinal section of the metacarpal bone showed minute opaque deposits between the trabeculae of cancellous bone in the metacarpal head and erosion of the metaphyseal compacta by tophi.

The pleural cavities contained small amounts

of clear fluid. The peritoneal cavity contained no excess fluid; the heart weighed 340 Gm.; its chambers were slightly dilated and the left ventricle measured up to 23 mm. in thickness. The coronary arteries were thin-walled and patent throughout. The aorta was narrow, elastic and showed no atherosclerotic changes. The lungs were congested and edematous posteriorly. The liver weighed 1,200 Gm. It was firm and covered by a thin translucent capsule. On section the lobular architecture was accentuated by congestion of the central veins. The left lobe of the liver was thin, flabby and appeared atrophic. The intrahepatic branches of the portal vein and all its main roots were dilated and lined by thick opaque intima. In the portal vein and in the adjacent portion of the splenic vein fibrous ridges projected about 1 mm. above the intimal surface criss-crossing in all directions. Between these ridges the vascular wall was thinner and bulged outward. The deepest pouch was situated on the anterior surface of the portal vein. It was 6 mm. deep and filled with firmly adherent yellow to dark red thrombotic material. Similar thrombi were present in the splenic vein close to its junction with the superior mesenteric vein, causing only slight stenosis of the lumen. Plaques of lime salt deposits were present in the portal and splenic veins between the aneurysmal bulges. The remainder of the splenic vein was tortuous and dilated averaging 4 cm. in circumference. The proximal portion of the superior mesenteric vein was 3 cm. in circumference and its smaller branches were dilated, tortuous and slightly sclerosed. The spleen was considerably enlarged and weighed 530 Gm. The capsule was thick, opaque, covered with hyaline plaques and adherent to the diaphragm. Cut surface was dry, flat, pink to red and traversed by numerous prominent trabeculae forming narrow spaces filled with firm pulp.

Gallbladder, adrenals and pelvic organs showed no important changes. There were no biliary calculi present.

The kidneys were of average size and each weighed 115 Gm. The capsules could be stripped with moderate difficulty revealing smooth surfaces. The left kidney was dark red with a few small yellow areas over the lower pole. Several small cortical cysts were present. The cortex averaged 4 mm. in width and showed the usual striations. The pyramids were congested and streaked white by gritty and granular deposits. Scattered through the cortex and pyramids were

multiple abscesses measuring 1 to 2 cm. in diameter. The right kidney was similar but generally paler. Renal pelvis and ureters showed no abnormality. No renal calculi were found.

The neck organs were not unusual. The vertebral column and the bones of the thoracic cage appeared unaltered and contained abundant dark red marrow. The external iliac lymph nodes were enlarged and soft. The cerebral arteries showed no arteriosclerosis.

Histologically, section of the heart showed mild hypertrophy and occasional basophilic degeneration of the myocardial fibers. Precipitated edema fluid was present in the alveoli in the posterior portions of the lungs. Sections from the right lobe of the liver revealed only mild congestion. In the left lobe dilated bile ducts were found surrounded by broad sheaths of fibrous tissue enclosing many small bile ducts and small scattered groups of liver cells. Neighboring liver lobules presented a normal appearance. No evidence of recent degeneration or necrosis of liver cells was found. The portal vein showed extensive changes in its wall. Intima and media were replaced by sclerosed fibrous tissue, irregularly intermingled with elastic lamellae. The fibrous tissue wall was fused with a laminated, hyalinized thrombus. In the adventitia thick bundles of smooth muscle were found arranged longitudinally along part of the circumference.

Sections of the spleen showed considerable thickening of the capsule and trabeculae by compact fibrous tissue. The malpighian corpuscles were few in number and the ones that remained were small and indistinct. The sinuses were empty, dilated and lined by prominent hyperplastic endothelium. The pulp was poor in cells and slightly fibrosed.

Sections of the kidney revealed several minute, narrow wedge-shaped, subcapsular scars with atrophy of the tubules, hyalinization of the glomeruli and interstitial fibrosis. Some of the atrophic tubules contained hyaline casts. The majority of the glomeruli were well preserved. The tubules were slightly dilated and contained a finely granular precipitate. The lining cells presented considerable postmortem changes. A few cortical cysts were lined by low cuboidal epithelium. The arterioles showed minimal thickening of the intima. Small and medium-sized arteries were of average caliber and their intima was slightly thickened by fibrous tissue. Scattered through pyramids and occasionally

extending into the inner half of the cortex were round or oval areas composed of a finely granular or fibrillar pale staining acidophilic material. (Fig. 3.) Small, irregular, empty spaces in this material indicated the presence of lipids and the acidophilic material often showed a radial star-like streaking. In some of these foci rhomboid, highly refractive and doubly refractive, pale yellow crystals were found lying singly, in irregular clusters or in sheaves. (Fig. 3.) Foreign body giant cells were attached to some of these crystals and surrounded smaller ones completely. At the periphery of these crystalline deposits a scant infiltrate of mononuclear cells was found. Mononuclears in radial arrangement also seemed to interdigitate with the radial striations previously mentioned.

Furthermore, focal abscesses were found in the parenchyma; some of them contained crystalline deposits and all of them were surrounded by an acute inflammatory reaction. Casts of polymorphonuclears were present in collecting tubules in these areas. A calyx showed severe inflammatory reaction; the surface epithelium was desquamated and loose and was mixed with polymorphonuclears and urate crystals. The mucosa was markedly congested and infiltrated with polymorphonuclear leukocytes and lymphocytes. Some kidney sections were stained according to the method of De Galantha.²⁹ (Fig. 4.) A starfish-like arrangement of black threads was thus revealed in the granular matrix previously described. Control stains for argyrophilic reticulum failed to demonstrate these structures, indicating that they were not reticulum fibers but urate crystals.

Section through the head of a metacarpal bone and the surrounding soft tissues (Figs. 5 and 6) revealed urate deposits in the articular cartilage, the cancellous bone of the capitulum and the metaphysis and in the periarticular structures. The surface of the hyaline cartilage was irregular, frayed and covered by granulation tissue (pannus) near the articular margins. Occasional deep fissures penetrated almost the entire thickness of the cartilage. Scattered through the hyaline cartilage were clusters of pale yellow, doubly refractive crystalline plates usually rhomboid in outline with longitudinal striations. Occasionally these crystals showed an arborescent arrangement. They lay close to the articular surface but were usually separated from it by a thin rim of apparently unaltered cartilage. The hyaline cartilage around these

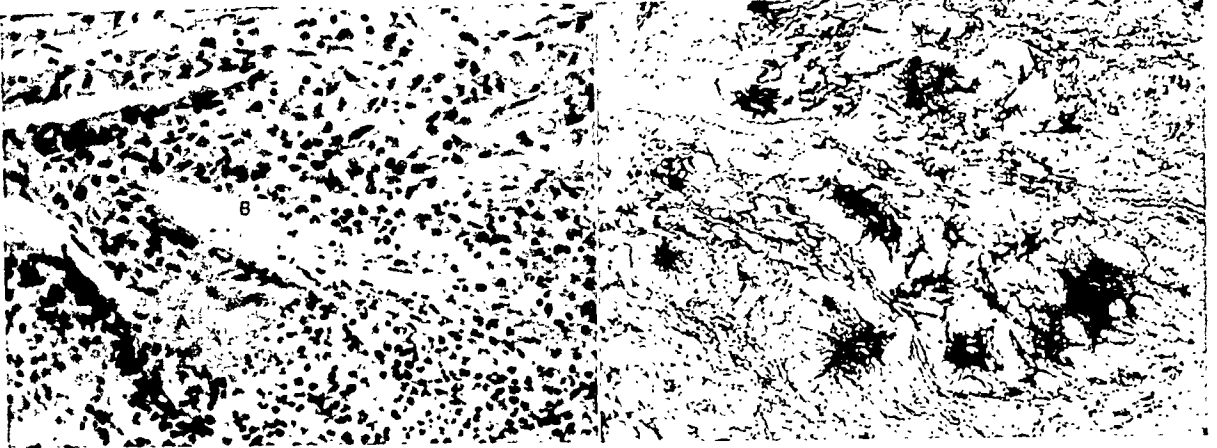


FIG. 3. A, water-soluble and B, water-insoluble urate crystals in the kidney. ($\times 552$.)

FIG. 4. Water-soluble urate crystals in the kidney stained black according to the method of E. De Galantha. ($\times 144$.)

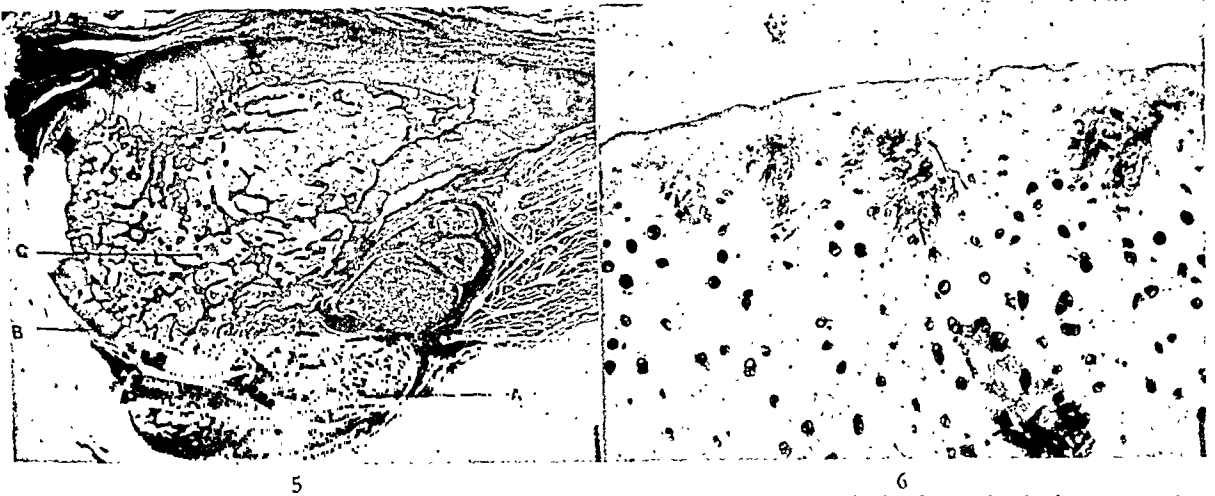


FIG. 5. Longitudinal section through the head of the metacarpal bone shows tophi in the periarticular connective tissue (A), and urate deposits in the articular cartilage (B), and in the bone marrow (C).

FIG. 6. Urate deposits in the articular cartilage. ($\times 144$.)

deposits showed no evidence of necrosis. The pannus covering the cartilage was also encrusted with urate deposits. On the volar aspect of the metacarpal head the cartilage was undermined by urate deposits which extended from large tophi in the capsular ligaments and the periarticular fibrous connective tissue. At one point the pannus bridged the articular space and attached the two opposing articular surfaces to each other. The osteocartilaginous border was sharp everywhere. The fibro-fatty marrow in the head and the distal metaphysis of the metacarpal bone contained urate deposits indicated by the eosinophilic matrix as seen in the kidneys. The crystals proper had apparently been dissolved and could not be seen in these sections that had been fixed in Zenker's solution and embedded in paraffin. Water-insoluble crystals were also present and were similar to those seen in the articular cartilage and in the kidneys.

In the periarticular tissue on the volar and dorsal aspects of the bone there were large tophi surrounded by fibrous tissue capsules. In these capsules and around small globules of urate deposits many foreign body giant cells and occasional large mononuclears could be seen. The smaller globules were composed principally of eosinophilic, granular or amorphous material, the matrix of soluble urate crystals. Small arteries and arterioles in the fibrous tissue around the joint showed mild to moderate fibrous intimal thickening.

The vertebral bodies contained highly cellular marrow, showing a slight preponderance of the erythropoietic elements. The bony trabeculae were unaltered. No urate deposits were present.

COMMENTS

Several features of this case warrant comment. One is the extensive involvement of

joints and subcutaneous tissues by urate deposits and secondary hypertrophic osteoarthritic changes. Occasional similar cases have been reported.^{3-10,19} Exhaustive descriptions of the lesions in the skeletal system and the periarticular structures have appeared in the literature; especially Pommer's description^{20,21} gives an excellent account of such morphologic changes as were observed in our patient. In all the cases reported extreme disabling lesions were found only many years after the first clinical symptoms had appeared. Usually gout first manifests itself in the fourth or fifth decade. Acute attacks of gouty arthritis are followed by complete remissions. During such remissions the patients feel perfectly well and in the beginning are able to carry on their usual occupation. Much later slight disability persists throughout the interval between attacks and after many years, sometimes ten, sometimes twenty or more, the joint lesions lead to complete invalidism. If the first attack occurs early in life, the articular lesions usually are more severe. It is therefore remarkable that although the patient experienced his first attack of joint pain at the age of forty-four the disease took such a devastating, rapidly progressive course and produced such extensive, crippling joint lesions in the comparatively short period of three years. Contrary to older concepts, gout is not uncommon in poorly nourished individuals who do not indulge in excessive food or alcohol intake.³ This patient showed no evidence and gave no history of antecedent overeating or obesity. Gout supposedly affects Orientals much less frequently than Europeans.²² Snapper does not even mention gout in his monograph on Chinese medicine.²³ Scattered reports of gout in Chinese, however, show that this race is not exempt.^{7,22,24}

Another remarkable feature was found in the morphology of the urate crystals since there were obviously two types of crystalline deposits in the tophi in cartilage, bones and kidneys. One type occurred in fine needles, usually in radial arrangement deposited in an acellular, finely granular or amorphous

eosinophilic matrix. Foreign body giant cells, lymphocytes and fibroblasts were found around these crystals. In preparations fixed in formalin, embedded in paraffin and stained with hematoxylin and eosin the crystals had disappeared and only their molds in the granular matrix remained. In order to demonstrate the crystals, fixation in absolute alcohol and staining according to the method described by De Galantha²⁵ were used. There were in addition other crystals which were plainly visible in formalin-fixed material, embedded in paraffin and stained with hematoxylin and eosin. They were, therefore, insoluble in water, alcohol and xylol; and since they also appeared in sections of bone decalcified with sodium citrate and formic acid, they were insoluble in weak acids. They were rhomboid in outline, doubly refractive, showed longitudinal striations and occurred in irregular clusters or sheaves of elongated blunt needles. Only one reference to these crystals was found in the literature.⁵ There it was suggested that the more recent urate deposits are water-soluble and the older deposits water-insoluble. Many of the standard textbooks on clinical pathology do not mention the morphologic detail and the physicochemical properties of these crystals at all or describe only one type.

The renal lesions were of particular interest since there was no clinical evidence of impaired renal function. Arteriolar nephrosclerosis and hypertension are considered common complications of gout.^{3,16} They were almost entirely absent in our patient. Only mild sclerosis of a few arterioles and small arteries was present and corresponding minute subcapsular scars were found. Although many observers believe that arteriosclerosis and nephrosclerosis are more common and appear earlier in gouty patients than in non-gouty people in comparable age groups,²⁶ the vascular changes and especially signs of renal failure appear late in the disease; however, a causal relationship of gout, nephrosclerosis and hypertension is by no means universally accepted.

Schnitker²⁶ claims that almost all gouty patients who die before the age of fifty and a significant percentage of those in the older age groups succumb because of this renal complication. Renal function tests on patients suffering from gout led Talbott³ to believe that the majority of patients with gout, irrespective of age or duration of symptoms, have impairment of renal function. The anatomic changes in the kidneys are usually those of vascular nephrosclerosis although they have been called vascular nephritis, chronic interstitial nephritis or gouty kidney—terms that should not be employed. Actually the lesions are indistinguishable from arterial and arteriolar nephrosclerosis as seen in benign hypertension. Occasionally chronic glomerulonephritis was found.¹⁰ The pathogenesis of the renal lesions is a matter of much dispute. They are attributed to the deposition of urates in the renal tubules and parenchyma by some,³ whereas others claim that the urate deposits can exist in the gouty kidney without manifestation of chronic nephritis and that they have in no way any causal relationship to the renal disease.²⁷ Observations in our patient tend to support at least the first half of the preceding statement. The concept of a higher incidence of arteriosclerosis and hypertension in gout than in a comparable group of people without gout is also not accepted by all observers. It is believed by some French authors especially that arteriosclerosis and gout do not have a cause and effect relationship but are rather the result of a disturbance of nutrition leading to gout and to arteriosclerosis.^{28,29} These authors even claim that arteriosclerosis and hypertension occur in the same percentage in gouty and non-gouty persons in the same critical age group, a statement that is diametrically opposed to the view held by Schnitker.²⁶ Thus, the French authors consider as highly exaggerated the opinion of those who like Huchard maintain that "gout is for the arteries what rheumatic fever is for the heart." But even if one accepts Schnitker's figures and the studies by Talbott³ and

others³⁰ on renal function in patients with gout, it does not necessarily follow that the deposits of urates in the kidney are the cause for extensive vascular sclerosis and renal damage. No detailed studies of renal function were attempted in our case, but routine urine and blood examinations did not suggest appreciable renal damage and still there were numerous urate deposits scattered through the renal parenchyma. It is conceivable that the total duration of the illness was too short for nephrosclerosis to develop. The deposition of urates in the kidneys *per se* did not lead to appreciable renal damage and in the course of several years development of hypertension and nephrosclerosis would not necessarily have to be interpreted as caused by gout. It should be remembered that gout is a hereditary constitutional disorder and that arteriosclerosis also is considered by some to have a hereditary or familial background.

Interstitial urate deposits in the kidney are usually not associated with severe inflammatory reaction. This patient, however, presented considerable acute and subacute pyelonephritis with abscess formation limited to the areas that contained the crystalline deposits. On the other hand, not all urate deposits were surrounded by abscesses or any other extensive inflammatory reaction. It may be assumed that the stagnation—an important factor in the development of pyelonephritis—was not uniform throughout the kidney. This is suggested by the presence of cellular debris mixed with polymorphonuclear leukocytes and urate crystals in some calyces and not in others.

The roentgenologic findings were not characteristic of gout.³¹ X-rays showed no specific changes as reported in the literature.^{3,4,6,15,19} In addition to periarticular soft tissue swelling, there were hypertrophic changes in the knee joints and tarsal bones.

Clinically, there was definite evidence of impaired liver function. No anatomic changes were found that would adequately explain this. The atrophy of the left lobe of the liver appeared to be old and involved too little liver parenchyma to cause a

clinically detectable change in liver function. Enlargement of the liver with tenderness and jaundice is occasionally present in gout.²² The enlargement is usually due to fatty change and chronic passive congestion. No fatty change was present in our patient nor was there appreciable congestion. No explanation can be given for this discrepancy.

The association of gout with splenomegaly and anemia deserves particular comment. Few similar cases have been reported.^{6,10,15,17,32} They present in most instances a fortuitous coincidence of gout and splenic anemia. Gout may appear sometimes during the course of pre-existing anemia with splenomegaly¹⁰ or the latter may intervene during the course of chronic gout.¹⁷ A complete autopsy was performed in only three of the cases reported. In two of them congenital hemolytic anemia was the associated disease¹⁰ and in the third the exact nature of the anemia and splenomegaly is not clear.⁶ Phlebosclerosis with calcification of the portal vein and its main tributaries with thrombosis, splenomegaly and anemia is not described in these reports. Phlebosclerosis of the portal vein has been the subject of many case reports.³³⁻³⁵ The lesion may be produced by a variety of causes or no cause at all may be apparent.³⁶ X-ray diagnosis of this condition was first described by Moberg.³⁷ In his case calcification had occurred in the thrombus rather than in the vessel wall. The association of gout with calcification of the portal vein might suggest that deposition of urates in the vessel wall had produced necrosis followed by lime salt incrustation. Urate deposits have been found at times in the most unusual locations such as the mitral valve.³⁸ However, we were unable to demonstrate urate crystals or their molds in the wall of the portal vein or its main tributaries. The etiology and pathogenesis of portal vein sclerosis and calcification remain obscure in this case. Discussion of splenic anemia in connection with portal vein sclerosis would go far beyond the

scope of this report and may be found in the relevant literature.

An interesting concept about the possible relationship between anemia and gout was suggested by Krafka.³⁹ He points out that any condition raising the maturation rate of red blood cells leads to increased uric acid output because more nuclei of immature red blood cells are extruded and metabolized. This rise in uric acid output was observed by Krafka in the course of experiments on dogs and by others^{11,12,40} in pernicious anemia during remission, spontaneous or induced. Krafka explains the association of lead poisoning and gout also on the basis of the anemia that is a constant feature of plumbism. He even attributes the disappearance of old fashioned gout of one hundred years ago to the discontinuance of the medical practice of bleeding since even small hemorrhages are marked hemopoietic stimuli. He also mentions one of Garrod's cases,¹⁶ a girl of ten who had her first attack of gout at the age of seven when she was suffering from anemia. It is conceivable that in our case the sclerosis of the portal vein, splenomegaly and anemia preceded the clinical manifestations of gout and that anemia was a precipitating factor. Anemia may provoke attacks of gouty arthritis, but it certainly is not the main etiologic factor since only few people suffering from anemia develop clinical gout. Gout must be considered as a disease developing on a constitutional hereditary basis in which anemia among other disturbances may precipitate the appearance of clinical symptoms.

SUMMARY

1. An unusual case of fulminating gout which occurred in a middle-aged Chinese male is reported. It was of remarkably short duration and exceptional severity, associated with phlebosclerosis, calcification and thrombosis of the portal vein, splenomegaly and anemia.

2. The unusual clinical and anatomic features of the gouty lesions are discussed.

3. The occurrence in the tophi of two types of urate crystals is described.

4. The extent and character of renal lesions are emphasized in the absence of clinical evidence of renal failure.

5. The association of gout and splenic anemia is discussed and reference is made to similar cases reported in the literature.

6. Suggestions in other reports about the possible relationship of anemia and gout are reviewed.

REFERENCES

1. McCracken, J. P., OWEN, P. S. and PRATT, J. H. GOUT: still a forgotten disease. *J. A. M. A.*, 131: 367, 1946.
2. HERRICK, W. W. and TYSON, T. L. Gout—a forgotten disease. *Am. J. M. Sc.*, 192: 483, 1936.
3. TALBOTT, J. H. Gout: From The Oxford Loose-Leaf Medicine. Vol. 4, pp. 79-134. New York, 1943. Oxford University Press.
4. MANIZADE, M. D. Ueber einen Fall von exzessiver Gicht mit besonderer Beruecksichtigung der Nierenveraenderungen. *Wien. Arch. f. inn. Med.*, 27: 301, 1935.
5. POMMER, G. Ueber das Vorkommen einer Harnsalzabart in Knochenmark- und Gelenkgicht-herden. *Beitr. z. path. Anat. u. z. allg. Path.*, 95: 92, 1935.
6. LAMBIE, C. G. and DAVIES, G. F. S. A case of chronic gout with anemia. *M. J. Australia*, 28: 701, 1941.
7. EAPEN, K. Report on a case of chronic advanced gout. *Malayan M. J.*, 11: 117, 1936.
8. LITTEN, M. Pathologisch-anatomische Beobachtungen. Ein Fall von schwerer Gicht mit Amyloiddegeneration. *Virchows Arch. f. path. Anat.*, 64: 129, 1876.
9. LUDWIG, A. O., BENNETT, G. A. and BAUER, W. A rare manifestation of gout; widespread ankylosis simulating rheumatoid arthritis. *Ann. Int. Med.*, 11: 1248, 1938.
10. DEITRICK, J. E. The association of congenital hemolytic jaundice and gout. *Internat. Clin.*, 3: 264, 1940.
11. SEARS, W. G. The occurrence of gout during the treatment of pernicious anemia. *Lancet*, 1: 24, 1933.
12. SPENCE, J. C. Liver and pernicious anemia. *Lancet*, 2: 1026, 1927.
13. LESCHKE, E. Haemolytischer Ikterus und Gicht. *Med. Klin.*, 13: 896, 1922.
14. OWEN, T. K. and ROBERTS, J. C. Acholuric jaundice and gout. *Brit. M. J.*, 2: 661, 1937.
15. LAMBIE, C. G. A study of juvenile gout in a patient suffering from chronic erythronoclastic anemia of obscure origin. Together with observations on the physical state of uric acid in the blood and the effect of splenomegaly. *M. J. Australia*, 27: 535, 1940.
16. GARROD, A. B. A Treatise on Gout and Rheumatic Gout (Rheumatic Arthritis). 3rd ed. London, 1876. Longmans, Green & Co.
17. FITZ, R. Three cases of intermittently painful joints, splenomegaly and anemia. *M. Clin. North America* 18: 1053, 1935.
18. ADAMS, E.¹⁰
19. FLANDIN, CH., POUMEAU-DELILLE, G. and ISRAEL, R. Un cas de goutte ulcérée du pied avec importantes destructions osseuses. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 52: 763, 1936.
20. POMMER, G. Von den Fruehstadien und den Rueckbildungsbefunden der gichtischen Harnsalzablagerungen. *Beitr. z. path. Anat. u. z. allg. Path.*, 90: 513, 1933.
21. ———. Mikroskopische Untersuchungen ueber Gelenkgicht. Gustav Fischer. Jena, 1929.
22. GRAFE, E. Die Krankheiten des Stoffwechsels und ihre Behandlung. Berlin, 1931. J. Springer.
23. SNAPPER, I. Chinese Lessons to Western Medicine. New York, 1941. Interscience Publishers, Inc.
24. DIEUAIDE, F. R.³
25. DE GALANTHA, E. Technic for preservation and microscopic demonstration of nodules in gout. *Am. J. Clin. Path.*, 5: 165, 1935.
26. SCHNITKER, M. A. and RICHTER, A. B. Nephritis in gout. *Am. J. M. Sc.*, 192: 241, 1936.
27. UMBER, F. Ernahrungs- und Stoffwechselkrankheiten. P. 379. Urban und Schwarzenberg. Vienna, 1914.
28. LIAN, C. and GILBERT-DREIFUS. L'appareil cardiovasculaire des gouteux. *Progrès méd.*, 2: 1613, 1935.
29. ABRAMI, P. and LICHTWITZ, A. Le rein gouteux. *Progrès méd.*, 2: 1617, 1935.
30. COOMBS, F. S., PECORA, I. J., THOROGOOD, E., CONSOLAZIO, W. V. and TALBOTT, J. H. Renal function in patients with gout. *J. Clin. Investigation*, 19: 525, 1940.
31. FERGUSON, A. B. Gout in roentgen diagnosis of the extremities and spine. *Am. J. Roentgenol.*, 17: 301, 1945.
32. VOLINI, I. F. Gout: a report of 10 cases for the year 1935. *M. Clin. North America*, 21: 3, 1937.
33. BRUGSCH, H. Die Klinik der Milzvenenerkrankungen. *Ergebn. d. inn. Med. u. Kinderh.*, 45: 43, 1933.
34. SPIEGELBERG, H. Verkalkung der Wandungen der thrombotischen Pfortader. *Virchows Arch. f. path. Anat.*, 142: 547, 1895.
35. SIMMONDS, M. Ueber Pfortadersklerose. *Virchows Arch. f. path. Anat.*, 207: 360, 1912.
36. REICH, N. E. Primary phleboscrosis. *Arch. Int. Med.*, 69: 117, 1942.
37. MOBERG, G. Calcified thrombosis of portal system diagnosed by roentgen examination. *Acta radiol.*, 24: 374, 1943.
38. BUNIM, J. J. and McEWEN, C. Tophus of mitral valve in gout. *Arch. Path.*, 29: 700, 1940.
39. KRAFKA, J., JR. A neglected factor in the etiology of gout. *J. Bone & Joint Surg.*, 17: 1049, 1935.
40. RIDDLE, M. C. and STURGIS, C. C. Endogenous uric acid metabolism in pernicious anemia. *J. Clin. Investigation*, 7: 498, 1929.

Friedländer's Bacillus Meningitis Treated with Streptomycin*

JOSEPH F. SADUSK, JR., M.D., ARNOLD S. RELMAN, M.D., ROBERT R. WAGNER, M.D. and ROY BARNETT, M.D.

New Haven, Connecticut

WHILE meningitis due to Friedländer's bacillus was first described some sixty years ago,¹ this disease still remains a clinical rarity. Ransmeier and Major,¹ after a careful survey of the literature up to 1943, could find only twenty-nine cases reported. They added another case. Since that time, twenty-three additional cases^{2-6,11-13,15} have been reported, only nine of them in detail. These cases include meningitis due to *Aerobacter aerogenes*, an organism which appears to be practically indistinguishable from Friedländer's bacillus.

The relative rareness of meningitis due to this group of organisms and the present meager experience with streptomycin treatment prompt the present report of a case of meningitis due to Friedländer's bacillus treated with this new antibiotic. Although the issue was fatal, the initial prompt clinical and bacteriologic response to streptomycin confirms previous favorable reports of its use in other types of infection due to this organism.

CASE REPORT

A sixty year old negress was admitted to the New Haven Hospital on November 12, 1946, with complaints of fever, chills, abdominal pain, vomiting and diarrhea. Except for symptoms of intolerance to fatty and greasy foods characterized by nausea and eructation, the patient had enjoyed good health until the present illness.

Two days before admission she suddenly felt chilly and shortly thereafter developed severe abdominal pain. This was at first localized to the epigastric region and to the right upper

quadrant but later radiated through to the back. She became nauseated and vomited large amounts of liquid material which was not grossly bloody. She passed watery stools at frequent intervals. Her family physician reported temperatures of 104°F. on the first and second days, and there were at least two shaking chills during this time.

Except for headache and prostration, there were no other symptoms of consequence. She became progressively worse and was admitted to the hospital late in the night of the third day of her illness.

On admission the patient looked acutely and desperately ill. She was enormously obese and obviously suffered extreme abdominal pain. The temperature was 102.4°F., pulse rate was 100, respiratory rate was 20 and blood pressure was 130/70. She was incontinent of feces and frequently passed dark brown, foul-smelling watery stools. The skin was warm and moist. There was no jaundice. Pupils were equal and reacted to light. There were no signs of meningitis. The thyroid was diffusely enlarged. No adenopathy could be found. The heart was not remarkable. There were a few medium, moist rales at both lung bases. Although the huge size of the abdomen made examination difficult, there was considerable generalized tenderness, with spasm in the right upper quadrant, and under the right costal margin posteriorly. Pelvic and rectal examinations were considered negative.

Examination of the blood revealed a red cell count of 5,300,000 per mm.³ and a hemoglobin of 13.0 Gm. per cent. Leukocytes were 16,500 per mm.³ The differential showed 92 per cent neutrophils (26 per cent of which were non-segmented forms), 6 per cent lymphocytes and 2 per cent monocytes. The urine was cloudy

* From the Departments of Internal Medicine and Pathology, Yale University School of Medicine, New Haven, Conn.

and amber, with an acid reaction; specific gravity, 1.010; albumin reaction, 3 plus and sugar, negative. Microscopic examination of the centrifuged sediment revealed 1 to 3 red cells and 20 white cells per high power field.

A fresh stool was described as a dark brown liquid with a 3 plus guaiac reaction. Microscopic examination revealed a moderate number of white cells but no cysts or parasites.

In view of the basilar pulmonary moisture, determinations of venous pressure and circulation time (arm to tongue with calcium gluconate) were performed; the values were 10 mm. saline and 17 seconds respectively. X-ray of the chest revealed a clear pulmonary parenchyma and a normal cardiac silhouette. X-ray of the abdomen revealed only hypertrophic osteo-arthritis of the lumbar spine. There was no significant dilatation of the intestinal loops, and neither abnormal soft tissue masses nor radio-opaque shadows in the region of the gallbladder were apparent.

Cultures of the blood, nasopharynx, urine, and stool were planted and the patient was given a slow venoclysis of 1,500 cc. of normal saline and 1,500 cc. of 10 per cent glucose solution. In the morning her temperature was 103.0°F. and there was no change in her general condition. The blood non-protein nitrogen was 78 mg. per cent, serum CO₂ content was 22.5 mEq. per liter and serum chloride was 92.7 mEq. per liter. Agglutination tests with *Bacillus typhosus* and *B. paratyphosus* A and B antigens were carried out and were subsequently reported negative. Although the Mazzini reaction was positive, the Kahn and Wassermann tests were negative.

At this time the blood culture drawn on admission was found to be strongly positive. In addition to growth in the broth the plate count showed about 1,300 colonies per cc. of a short, thick, gram-negative encapsulated bacillus. The surface colonies were smooth, greyish-white and mucoid in appearance. Nose, throat, urine and stool cultures revealed the presence of a similar-appearing organism.

The patient's grave condition made it imperative to begin chemotherapy without waiting for further identification of the pathogen. Another blood culture was taken and a rapid infusion of 500 cc. of normal saline containing 5.0 Gm. of sodium sulfadiazine was administered. Four hours later the patient had a shaking chill and her temperature rose to 105.8°F. Another blood

culture was obtained shortly after the chill. The blood sulfadiazine level was 8.8 mg. per cent at this time. The patient became semicomatose and was incontinent of urine and feces. For the first time her neck was noted to be slightly stiff. Lumbar puncture yielded turbid fluid under an initial pressure of 300 mm. spinal fluid. It contained 700 white cells per cu. mm., 90 per cent of which were polymorphonuclear leukocytes. The total protein concentration was 117 mg. per cent. The sediment was loaded with what appeared to be the same organism previously seen in all the cultures.

By this time the organism in the first blood culture had been identified as Friedländer's bacillus, type B, by means of a positive quellung reaction with type-specific antiserum. In view of this sulfadiazine therapy was discontinued and the patient was started on streptomycin. A blood culture taken at this time revealed approximately the same number of organisms present prior to administration of sulfadiazine. One-half Gm. of streptomycin was administered intramuscularly every four hours and 50 mg. was injected intrathecally after removal of an appropriate amount of cerebrospinal fluid. Intramuscular injection of ½ Gm. every four hours, plus a daily intrathecal injection of 50 mg. was continued for the remainder of her brief course.

Figure 1 indicates the patient's subsequent progress. To be noted particularly are the rapid fall in temperature and the striking effect on the bacteriologic findings. Thirty-six hours after streptomycin had been started the temperature was normal and the patient appeared much better. After the initial intrathecal dose culture of the cerebrospinal fluid was sterile although a few organisms were seen on smear. On the following day both smear and culture were negative for the organisms and the last two samples of blood, drawn forty-eight and sixty hours after the start of streptomycin, were sterile.

Despite her clinical improvement, however, the patient's non-protein nitrogen continued to rise and she developed a mild acidosis. On the last day of life her CO₂ content was 17.4 mEq. per liter and the non-protein nitrogen was 119 mg. per cent. Urine output was adequate.

On the morning of the sixth day of the disease the patient had another shaking chill and her temperature rose rapidly to 104.2°F. She became comatose. The blood pressure dropped to 88/45.

There were no new physical signs. An infusion of 300 cc. of whole citrated blood, 500 cc. of plasma and 2,000 cc. of saline and glucose solution brought the blood pressure back up to previous levels. The patient remained comatose and expired late that night after developing signs of congestive heart failure.

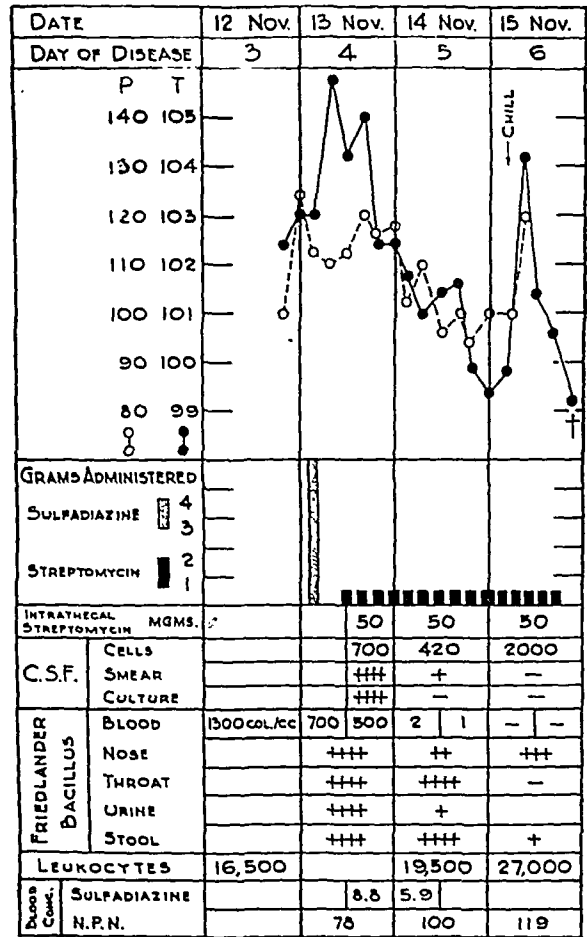


FIG. 1. Clinical and laboratory data in case of Friedländer's bacillus meningitis.

The stool cultures were of unusual interest. Initially they yielded a pure growth of an organism indistinguishable from Friedländer's type B bacillus isolated from the blood, cerebrospinal fluid, nose, throat and urine, except for the following points: (1) fermentation of dulcitol with the production of gas and acid, (2) a positive indol reaction and (3) the absence of capsular swelling with type-specific A or B Friedländer's antiserum. Later cultures contained fewer of these organisms but there was a heavy growth of *Escherichia coli*. Biochemical reactions of the former organism are compared in Table 1, with the organisms isolated from the

blood, spinal fluid, nose, throat and urine.* Table 1 summarizes the cultures made during the patient's life.

The organisms isolated from the other cultures all gave a positive reaction with type B Friedländer antiserum and exhibited most of the biochemical reactions usually attributed to Friedländer's bacillus. Streptomycin sensitivity determinations on the organism recovered from the blood on the third and sixth days of the disease showed that there was no significant change. The sensitivity at first was 16 micrograms per cc.; later it was 14 micrograms per cc.

Only those lesions found at autopsy and which are relevant to the last illness are described. Others are enumerated in the final anatomical diagnosis.

In the dome of the right lobe of the liver, lateral and posterior to the inferior vena cava, was a large abscess 10 cm. in diameter. There was a thin fibrous capsule from which friable fronds of tissue projected into thick pink-yellow pus. In the adjacent hepatic vein there was a large, flat, pink, adherent mural thrombus which narrowed the lumen of the vein only slightly. It reached within 1 cm. of the vena cava. Microscopically, the abscess wall was partly organized; the abscess contained necrotic liver tissue and pus as well as many Friedländer's bacilli. The thrombus was made up of fibrin, platelets and leukocytes but no bacteria. The underlying vein wall was partly disorganized but not necrotic.

The gallbladder wall was thickened to an average of 3 mm.; the mucosa was granular and there were three large calculi in the lumen. Microscopically, there were some lymphocytes but no polymorphonuclear leukocytes in the wall. The bile ducts were not dilated and contained no calculi.

The right kidney weighed 305 Gm. There were small scars in the pyramids as well as diffuse interstitial edema and necrosis of tubular epithelium. The left kidney was shrunken and deformed, weighing 135 Gm. The upper two-thirds was fibrotic with blunting of the papillae and enlargement of the calyces. The main artery to this area was thick-walled but not occluded. Microscopically, a thyroid pattern of dilated tubules filled with colloid casts was associated with marked hyperplastic arteriosclerosis and

* The authors are indebted to Miss Eleanora Falco, Technical Assistant, Yale University School of Medicine for the studies carried out upon the isolated organisms.

TABLE I

BIOCHEMICAL REACTIONS OF THE ORGANISM ISOLATED FROM THE BLOOD, SPINAL FLUID,
NOSE, THROAT, URINE AND STOOL

	Blood	Spinal Fluid	Nose	Throat	Urine	Stool
Lactose.....	AG	AG	AG	AG	AG	AG
Dextrose.....	AG	AG	AG	AG	AG	AG
Sucrose.....	AG	AG	AG	AG	AG	AG
Maltose.....	AG	AG	AG	AG	AG	AG
Mannite.....	AG	AG	AG	AG	AG	AG
Xylose.....	AG	AG	AG	AG	AG	AG
Dulcitate.....	Sl.A	Sl.A	—	Sl.A	Sl.A	AG
Salicin.....	AG	AG	AG	AG	AG	AG
Litmus milk.....	A	A	A	A	A	A
Kligers.....	Slant: A Butt: AG	Slant: A Butt: AG	Slant: A Butt: AG	Slant: A Butt: AG	Slant: A Butt: AG	Slant: A Butt: AG
Indol.....	—	—	—	—	—	+
Methyl red.....	—	—	—	—	—	—
Voges-Proskauer.....	—	—	—	—	—	—

TABLE II

SUMMARY OF BACTERIOLOGIC FINDINGS

Blood.....	11/12/46 (midnight) 11/13/46 (9 A.M.) 11/13/46 (1 P.M.) 11/14/46 (9 A.M.) 11/14/46 (5 P.M.) 11/15/46 (9 A.M.) 11/15/46 (5 P.M.)	1,300 colonies/cc. of Friedländer's bacillus, type B 700 colonies/cc. of Friedländer's bacillus, type B 500 colonies/cc. of Friedländer's bacillus, type B 2 colonies/cc. of Friedländer's bacillus, type B 1 colonies/cc. of Friedländer's bacillus, type B No growth No growth
Spinal fluid.....	11/13/46 11/14/46 11/15/46	Heavy growth, Friedländer's bacillus, type B No growth No growth
Nose.....	11/13/46 11/14/46 11/15/46	Heavy growth, Friedländer's bacillus, type B Light growth, Friedländer's bacillus, type B Moderate growth, Friedländer's bacillus, type B
Throat.....	11/13/46 11/14/46 11/15/46	Heavy growth, Friedländer's bacillus, type B Heavy growth, Friedländer's bacillus, type B; scant growth, <i>Staphylococcus albus</i> Moderate growth, <i>Staphylococcus albus</i>
Urine.....	11/13/46 11/14/46	Heavy growth, Friedländer's bacillus, type B Scant growth, Friedländer's bacillus, type B
Stool.....	11/13/46 11/14/46 11/15/46	* Heavy growth, Friedländer's bacillus * Heavy growth, Friedländer's bacillus; heavy growth, <i>E. coli</i> * Scant growth, Friedländer's bacillus; heavy growth, <i>E. coli</i>

* Type-specific serum failed to produce capsular swelling with this organism.

productive endarteritis as well as edema and round cell infiltration of the submucosa of the pelvis.

In the first part of the duodenum there was a small depressed scar made up of fibrous tissue and a few lymphocytes with an intact overlying mucosa. There was slight clouding of the meninges in the sulci over the cerebrum and around the base of the brain, reflected histologically by small accumulations of leukocytes. No gross or microscopic evidences of cerebritis or cerebral abscess were found. The spinal cord was not examined.

Postmortem cultures were reported as follows: Liver abscess, many colonies of Friedländer's bacillus; heart's blood, two colonies of Friedländer's bacillus per cc.; gallbladder bile, no growth.

Anatomic diagnoses were: Primary: Chronic cholecystitis and cholelithiasis; chronic pyelonephritis, bilateral; atrophy of the left kidney; hypertrophy of the right kidney; liver abscess, thrombus in the right hepatic vein;* acute meningitis; acute splenic tumor; pulmonary congestion; cloudy swelling of the viscera. Subsidiary: Syphilitic aortitis; mural thrombus of aorta; chronic aortic valvulitis; cardiac dilatation; myocardial scars; focal fibrosis of the lungs; fibrous pleural adhesions; hyperplasia of the thyroid gland; fibromyoma of the uterus; obesity.

The liver abscess was obviously older than the history had indicated. The original source of infection could have been the chronic pyelonephritis or more likely the chronic cholecystitis; less probably, the fibrous scars in the duodenum or lungs. It is also possible that an enteric focus which healed without residua was responsible, this ordinarily being the most common explanation for single pyogenic liver abscesses. The hepatic vein thrombus was doubtless the source of further dissemination of the organisms to the blood and meninges. No explanation of the sudden death after preliminary improvement was afforded by the autopsy, the syphilitic disease of the aortic valve and aorta being minimal.

COMMENTS

Based upon the summary of the thirty cases previously prepared by Ransmeier and Major¹ and the twenty-three cases

reported by others^{2-6,11-13,14} this case of meningitis due to Friedländer's bacillus brings the total of reported cases of this disease to 54. As previously noted and commented upon in greater detail further, meningitis due to *Aerobacter aerogenes* is also included in this group. Some pertinent facts about these cases are summarized in Table III.

The age distribution is of particular interest. Eleven instances were found in infants one year of age or less, three cases were found in the third year of life and, with the exception of two cases occurring between the ages of ten and nineteen, the remaining twenty-four cases for which exact age data are given fall in the group of those past twenty years of age.

Study of sex distribution brings out an apparent predilection of the disease for males. In forty-nine cases thirty-seven were stated to be males and twelve were females.

Analysis of the probable portal of entry of the organism into the blood stream and subsequently the subarachnoid space (although in some instances the subarachnoid space may have been entered primarily) does not indicate any essential difference between the infant and adult groups. The most common portal of entry would appear to be through penetrating wounds of the central nervous system or infections of the upper and lower respiratory systems. Otitis and mastoiditis are other common sources of infection. Less commonly the organism may invade through the gallbladder, the uterus or the urinary tract. In approximately one-fifth of the cases the portal of entry is not known or is not described.

In addition to the typical clinical findings of acute meningitis examination of the cerebrospinal fluid presents the picture of an acute purulent meningitis with cloudy, thick fluid under increased pressure. The cellular response is predominately polymorphonuclear in type, and smear and culture of the fluid for organisms of the Friedländer's—*Aerogenes* group are usually positive. For instance, in twenty-eight of the cases wherein note was made concern-

* Clinically, B. Friedländeri type B septicemia.

ing identification of organisms by smear, the smear was positive in twenty-three instances. Culture of the cerebrospinal fluid revealed the organisms in twenty-five of twenty-seven cases.

one of meningitis secondary to a unilateral mastoiditis and subdural abscess. The meningitis spontaneously subsided after drainage of the subdural abscess. Since then, reports have appeared describing

TABLE III

SUMMARY OF FIFTY-FOUR REPORTED CASES OF FRIEDLÄNDER'S BACILLUS MENINGITIS*

Age (in years)	0-1 11	6-9 0	40-49 3	Not stated exactly: 14
	1-2 0	10-19 2	50-59 5	
	2-3 3	20-29 5	60-69 2	
	4-5 0	30-39 6	70-79 3	
Sex	Male: 37	Female: 12	Not stated: 5	

Portal of Entry

Focus	Age 3 or Less	Age over 3	Age Unknown	Total
Otitis, mastoiditis	1	7	0	8
Pneumonia, bronchitis	5	3	0	8
Paranasal sinuses	0	5	0	5
Cholecystitis	0	2	0	2
Uterine infection	0	2	0	2
Pharyngitis	0	1	0	1
Arthritis	1	0	0	1
Urinary tract	1	0	0	1
Wounds or operations on central nervous system	0	14	0	14
Other wounds	0	1	0	1
Unknown	6	3	2	11
	14	38	2	54

Bacteriology—Blood (antemortem): Culture positive in 12 of 18 cases

Cerebrospinal fluid: Smear positive in 23 of 28 cases; culture positive in 25 of 27 cases

Prognosis—Positive blood culture: All 12 patients died; negative blood culture: in 6 patients, 2 survived

* Published data incomplete for some of these patients.

In eighteen cases in which antemortem culture of the blood was performed such culture was positive in twelve instances. All of the patients in this group died. Of the remaining six patients with negative blood cultures two survived.^{8,9}

Only five survivals have been reported: the two patients with negative blood cultures just noted, and three additional cases recently reported by Mori,² Paine et al.⁶ and Montes¹¹ in which information was not given concerning blood culture.

Specific Therapy. Before the advent of chemotherapy, examination of the literature on Friedländer's bacillus and *A. aerogenes* meningitis revealed only one instance in which recovery took place. This case, reported by Rothschild⁷ in 1931, was

the treatment of this disease with sulfanilamide,¹ sulfapyridine⁸⁻¹⁰ sulfadiazine,³⁻⁴ penicillin and streptomycin separately or together^{2,5,6,12,13} and penicillin with sulfonamides.^{5,14} These reports further indicate that four recoveries have taken place following specific therapy: two cases with sulfapyridine,^{8,9} one case with sulfadiazine,³ and one case with streptomycin therapy.⁶

In addition to these four recoveries Tartakoff, Grynbaum and LeCompte² have described a patient treated with streptomycin; this treatment resulted in apparent bacteriologic cure although the patient eventually died of pulmonary embolism. To date a total of eight patients have been treated with streptomycin, with but one

recovery. In several instances the drug was not started until late in the course of the disease and may not have had a fair trial. In three of the patients no data on dosage are available. Analysis of the recovered patients reveals nothing of significance with respect to age, sex or portal of entry. However, it is of interest to point out again that not a single recovery has resulted from this type of meningitis in which the blood culture was initially reported to be positive. Results of blood culture were described in two of the recovered patients. In both instances the blood cultures were negative.

Streptomycin has a potent effect upon experimental infections caused by Friedländer's bacillus,¹⁵ and it has been reported as extremely effective in a variety of other infections in the Friedländer-Aerogenes group.¹³ It would appear that this new antibiotic may be the present treatment of choice for meningitis due to these organisms. A daily dose of 4.0 gm. administered intramuscularly at intervals of from four to six hours supplemented by an intrathecal administration of 50 mg. of the drug once a day may eradicate bacilli from the blood and cerebrospinal fluid.

Bacteriology. The differentiation of Friedländer's bacillus from *A. aerogenes* is extremely difficult and sometimes impossible. Occasionally one cannot even separate these organisms from *E. coli*.¹⁰ For clinical purposes it is necessary in the light of present knowledge to consider *B. Friedländer* and *A. aerogenes* in one group despite the fact that the former organism may be serologically divided into a number of types. The Friedländer-Aerogenes organisms are gram-negative bacilli with well defined capsules which produce luxuriant, raised, non-pigmented, mucoid and stringy colonies on solid media. They do not liquefy gelatin. Their biochemical reactions are exceedingly variable and even serologically identical strains may sometimes yield different tests.

These problems are well illustrated by the variable reactions of the organism isolated from our patient. (Table I.) Although

capsular swelling was readily obtained by Friedländer type B antiserum with the strains isolated from the blood, cerebrospinal fluid, nose, throat and urine, such reaction could not be demonstrated with the organism isolated from the stool. Biochemical peculiarities such as indol production, dulcitate fermentation and methyl red reaction are presented in Table I for strains of the organism isolated from various body cavities.

SUMMARY

A fatal case of type B Friedländer's bacillus meningitis, septicemia, cholecystitis and liver abscess in a sixty year old female is reported. Although intramuscular and intrathecal therapy with streptomycin resulted in striking bacteriologic improvement, the patient suddenly died on the sixth day of the disease from an undetermined cause. This brings the total reported cases of Friedländer-Aerogenes meningitis to fifty-four. Before the advent of chemotherapy only one recovery was reported; since then, four additional recoveries have been reported in which the sulfonamides or streptomycin have been used.

Intramuscular and intrathecal administration of streptomycin is probably the treatment of choice although only one of several patients treated in this fashion has survived.

REFERENCES

1. Ransmeier, J. C. and Major, J. W. Friedländer's bacillus septicemia and meningitis. Report of a case and autopsy, with an analysis of twenty-nine cases collected from the literature. *Arch. Int. Med.*, 72: 319-328, 1943.
2. Tartakoff, S., Grynbaum, B. and LeCompte, P. M. Friedländer bacillus meningitis treated with streptomycin. *New England J. Med.*, 235: 681-683, 1946.
3. Mori, G. E. Meningitis a neumbacilo de Friedländer en un niño de veintiseis meses, curada. *Rev. Soc. pediat. de Rosario*, 8: 113-121, 1943.
4. King, S. J. Friedländer's bacillus meningitis with report of case treated unsuccessfully with sulfadiazine. *Ann. Int. Med.*, 24: 272-277, 1946.
5. Hough, P. T. and Adelson, L. Meningitis caused by Friedländer's bacillus or *Aerobacter aerogenes*. Report of two cases with autopsies. *Am. J. Clin. Path.*, 17: 534-537, 1947.

6. PAINE, T. F., MURRAY, R., SEELER, A. O. and FINLAND, M. Streptomycin in the treatment of meningitis: Report of 27 cases treated at the Boston City Hospital. *Ann. Int. Med.*, 27: 494-518, 1947.
7. ROTHSCHILD, K. Meningitis caused by Friedländer's bacillus. A case with recovery. *J. A. M. A.*, 97: 1956-1959, 1931.
8. ROBERTSON, C. W. Meningitis due to *B. friedlanderii*: recovery of a case treated with sulfapyridine. *Canad. M. A. J.*, 45: 70-71, 1941.
9. MONTES, G. G. and REAL, W. A. Meningitis purulenta a neumobacilo de Friedländer (*Klebsiella pneumoniae*) curado con dajenan. *Bol. Soc. cubana de pediat.*, 12: 5, 1940.
10. OSTERMAN, E. and RETTGER, L. F. A comparative study of organisms of the Friedländer and coli-aerogenes groups. I. Morphological and cultural characteristics with emphasis on variation. *J. Bact.*, 42: 699-719, 1941.
11. NEILL, C. L. and BLECHMAN, H. F. *Aerobacter aerogenes* meningitis. *Bull. U. S. Army M. Dept.*, 7: 722, 1947.
12. DEBAKEY, M. and PULASKI, E. J. An analysis of the experience with streptomycin therapy in U.S. army hospitals. *Surgery*, 20: 749-760, 1946.
13. National Research Council Committee on Chemotherapeutics and Other Agents. Streptomycin in the treatment of infections. *J. A. M. A.*, 132: 4, 70, 1946.
14. SOLOMON, S. Wound infections with Friedländer bacillus followed by meningitis. *New England J. Med.*, 237: 149, 1947.
15. HEILMAN, F. R. Streptomycin in the treatment of experimental infections with micro-organisms of Friedländer group. *Proc. Staff Meet., Mayo Clin.*, 20: 33-39 (Feb. 7) 1945.

Heart Block and Leukemic Cell Infiltration of Interventricular Septum of Heart*

DAVID T. DRESDALE, M.D., DAVID SPAIN, M.D. and FLORENTINO PEREZ-PINA, M.D.
New York, New York

A CAREFUL review of the literature revealed only two instances of patients with leukemia who had 2:1 heart block^{1,2} and no reports of patients with leukemia and complete heart block. The paucity of literature on heart block in patients with leukemia and without other etiologic factors has prompted this report.

CASE REPORT

The patient was a forty-four year old, married, white, male carpenter who was admitted to Bellevue Hospital with the chief complaint of a sharp pain of five days duration which was aggravated by motion, shooting down the back of his left leg. His present illness began insidiously about six weeks before admission when he contracted a severe cold. Shortly thereafter he noticed that his gums were soft, sore and bled easily and that he tired more readily. Two weeks later he had "quinsy" sore throat which was treated by his local physician. At this time he began to have vague chest pains and exertional dyspnea which became progressively worse. The sciatic type of pain which brought the patient to the hospital began suddenly while he was lying in bed and it was so severe that he was unable to leave his bed. Two days prior to admission he became aware of some swelling of his ankles and hands. His past history was essentially negative except for gonorrhea at the age of nineteen and a rather indefinite history of asymptomatic hypertension for three or four years before his present illness. The family history was non-contributory.

Physical examination on admission showed a well developed and well nourished white man who appeared chronically ill. He was comfortable only when he lay still. His skin was pale and sallow. There was generalized subcutaneous edema, including the face, and small areas of

ecchymoses in the right axilla and on the posterior surface of the left arm. Conjunctivae were pale. Fundi showed recent hemorrhage and exudates. Gums were markedly hypertrophied, infected at tooth margins and crusted with blood. The tonsils were enlarged and there was a grayish ulceration at the lower pole of the right tonsil. There was generalized lymphadenopathy; none of the nodes, however, were larger than 3 to 5 mm. in diameter. There was a slight increase in the anteroposterior diameter of the chest. There were dullness, some suppression of breath sounds and a few medium moist rales at the base of left lung, posteriorly. The heart was slightly enlarged to the left; the place of maximum impulse was in the fifth interspace just lateral to the mid-clavicular line. Sounds were of fair quality. The heart action was regular, with a ventricular rate of 88 that was equal to the pulse rate. A grade II systolic murmur was heard over the precordium, loudest at the apex. P₂ was louder than A₂. The liver edge, firm, smooth and not tender, was felt two finger breadths below the costal margin. The spleen was not palpable. There was spasm of the low back muscles and great tenderness over the course of the left sciatic nerve. Any form of motion of the left hip elicited severe pain.

A provisional diagnosis of acute leukemia with leukemic infiltration or hemorrhage to involve the left sciatic nerve was made on admission.

Laboratory studies showed: hemoglobin, 6.5 Gm (Sahli); red blood cell count, 1.94 million; white blood cell count, 95,800 with 24 per cent neutrophils, 11 per cent lymphocytes, 2 per cent monocytes, 60 per cent "blasts," 3 per cent myelocytes; platelets 110,000. In spite of frequent transfusions the hemoglobin never was found to be higher than 9 Gm. and the red blood cells, 2.84 million. The differential count remained unchanged. Repeated urinalysis was

* From the Department of Medicine, Columbia University, College of Physicians and Surgeons; and the First Medical Division, Bellevue Hospital, New York, N. Y.

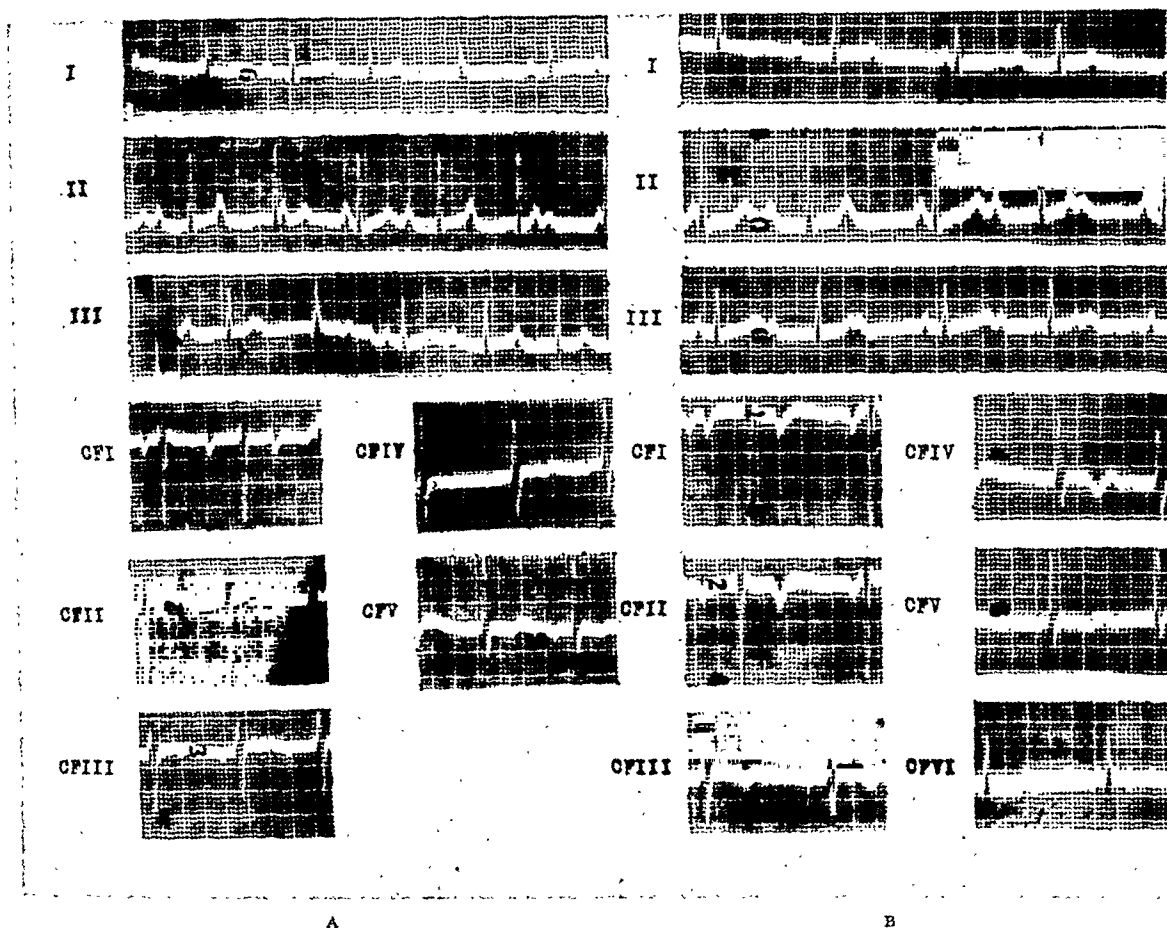


FIG. 1. Patient A. M. K. A, January 27, 1947; electrocardiogram six days after admission showing complete auriculoventricular dissociation. B, February 2, 1947; electrocardiogram six days later showing complete auriculoventricular dissociation and inversion of T waves in CFI, II, III and IV.

negative except for one plus albumin and occasional white blood cells and granular casts in the sediment. Blood uric acid on three occasions was 3.7 mg. per cent, 6.2 mg. per cent and 7.5 mg. per cent, respectively. Serum proteins on two instances were 4.7 Gm. per cent (A/G = 1.1 Gm. per cent/3.6 Gm. per cent) and 5.7 Gm. per cent (A/G = 2.1 Gm. per cent/3.6 Gm. per cent). Electrocardiogram (Fig. 1A) on January 27, 1947, six days after admission, showed complete auriculoventricular dissociation, with an auricular rate of 100 per minute and a ventricular rate of 82 per minute. Duration of QRS equalled .08 second; electrocardiogram (Fig. 1A) repeated on February 2, 1947, continued to show complete auriculoventricular dissociation. The auricular rate was 94 per minute and the ventricular rate was 62 per minute. Duration of QRS equalled .10 second. The T waves showed progressive changes, now being deeply inverted in CFI, CF₂, CF₃, and diphasic in CF₆ and CF₇.

The patient's temperature fluctuated between 100 and 101°F. On the third hospital day the spleen could be felt at the left costal margin. The patient appeared to improve objectively as well as subjectively. The pain in his left hip and leg subsided at the end of the first week. Therapy consisted mainly of blood transfusions and penicillin. On the twenty-first hospital day the patient suddenly became apneic and gasped two to three times a minute; his pupils dilated widely and he appeared to be *in extremis*. Oxygen and artificial respiration were administered immediately and the patient regained consciousness, vomited and perspired profusely. Several hours after that episode he seemed to be his usual self. Two days later he was found dead in his bed.

The post-mortem findings (necropsy No. 35032) will be limited to those pertinent to this report. The heart weighed 400 Gm. The pericardium was smooth and glistening. All of the valves were delicate and competent. In places

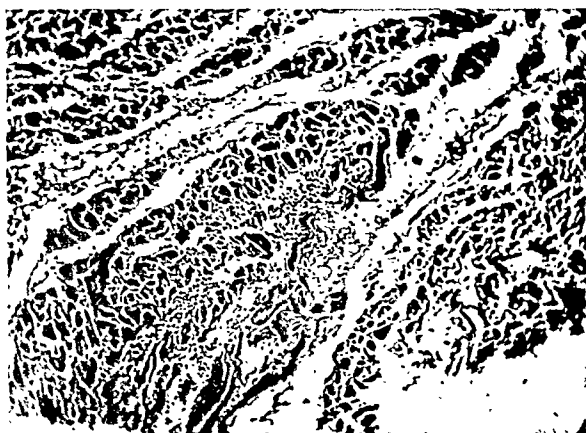


FIG. 2. Photomicrograph of section of interventricular septum in the region just below the undefended space, showing leukemic cell infiltration, focal atrophy and fibrosis of the myocardium; hematoxylin and eosin, $\times 150$.

the myocardium appeared somewhat pale but there were no definite areas in the gross suggestive of leukemic infiltration. The left ventricular myocardium measured 1.7 cm.; the right ventricular myocardium measured 0.6 cm. The coronary ostia were patent and the coronary arteries contained occasional small cholesterol plaques. There was no narrowing or occlusion of the coronary arteries. In the aorta there were a few small atherosclerotic plaques. The liver weighed 2,750 Gm. and its lobular architecture was accentuated. The spleen weighed 630 Gm., was firm and the pulp was dark red. Several small infarcts were present. The right kidney weighed 250 Gm. and the left kidney weighed 300 Gm. There was diffuse, yellowish mottling throughout the cortex and medulla. The mesenteric lymph nodes were enlarged to 3 or 4 cm. in diameter and were firm and grayish-white on section. The remainder of the lymph nodes throughout the body varied in size from 0.5 cm. to 2 cm. in diameter and were similar in appearance to the mesenteric nodes. The bone marrow was dry and presented a pale grayish-pink surface. There were no other significant findings.

Several sections through the interventricular septum of the heart, particularly those beneath the undefended space, revealed both focal and diffuse areas of leukemic cell infiltration (myeloid series). (Fig. 2.) Wherever these cells were present there was some degree of atrophy of the myocardial fibers and, in places, fibrous tissue replacement. The remainder of the myocardium did not contain any leukemic cell infiltration and revealed no other unusual changes. The

liver, spleen, lymph nodes, bone marrow, lungs, intestinal tract, kidneys and gums were the sites of leukemic cell infiltration similar to that seen in the myocardium.

The final anatomic diagnosis was acute myeloid leukemia with involvement of lymph nodes, bone marrow, spleen, liver, lungs, alimentary tract, interventricular septum of heart, kidneys and gums; infarcts of spleen; atherosclerosis of aorta, minimal.

COMMENT

Of the two patients reported with leukemia and 2:1 heart block, demonstration of leukemic infiltration microscopically was possible in only one of them since necropsy permission was not granted in the other. It was assumed that leukemic infiltration of the septum was the underlying cause of the 2:1 heart block in the latter patient, a sixty-four year old white woman with long-standing hypertension who developed chronic myelogenous leukemia because the heart block was made to disappear for short periods after x-ray therapy was directed to the cardiac area. Aronson and Leroy,¹ in addition to the patient with the 2:1 heart block, presented seven other patients with leukemia in whom, microscopically, changes in the heart secondary to leukemia could be demonstrated. The changes consisted of one or a combination of the following: (1) leukemic infiltration in various layers of the heart, (2) engorgement of the capillaries with immature white cells, (3) recent small foci of interstitial hemorrhage and (4) severe fatty degeneration. Six of the eight subjects had manifested signs of heart disease and had abnormal electrocardiograms.

Leukemic infiltration of the myocardium is not an uncommon observation.³⁻⁵ Kirschbaum and Preuss,³ in going over 14,400 consecutive autopsies, found 123 cases of leukemia; of these, the heart was the second most commonly involved organ. They found leukemic cells in the capillaries and in the interstitial tissue between the myocardial fibers in forty-three (34 per cent) of the patients. Unfortunately, electrocardiographic studies were not reported in any

of these although seven of the cases were diagnosed clinically as either rheumatic or arteriosclerotic heart disease.

The reason for so few reports on heart block in patients with leukemia is not clear. It would seem that with the high percentage of cardiac involvement in leukemia, there should be more instances of heart block. Complete and 2:1 heart block could be overlooked on physical examination, especially in those cases in which there are normal pulse and ventricular rates. A ventricular rate of 70 to 90 with heart block in subjects who are anemic and/or febrile, as is frequent in patients with leukemia, would not be unusual. The patient in this report had a regular ventricular rate of 88 per minute on admission and a rate of 82 per minute as recorded by electrocardiogram six days later. The auriculoventricular dissociation was not suspected on admission and was discovered only after the electrocardiogram was taken. It is of interest to note that at the time of the second electrocardiogram, when the anemia had been improved somewhat by transfusions, the ventricular rate was 62 per minute, a rate suggestive of some degree of heart block. Perhaps routine electrocardiograms on patients with leukemia would demonstrate more instances of disturbance of the conduction mechanism as well as other abnormalities of the myocardium.

SUMMARY

A case report is presented, including post-mortem findings, of a patient with acute myeloid leukemia and heart block. There was no narrowing or occlusion of the coronary arteries.

Histologic examination of sections of interventricular septum of the heart revealed leukemic cell infiltration, focal atrophy and fibrosis of myocardium. The remainder of the myocardium was not involved in this process. The leukemic cell infiltration of the interventricular septum of the heart was probably the primary etiologic factor in the disturbance of the conduction mechanism.

It is suggested that perhaps routine electrocardiograms would reveal more instances of heart block in patients with leukemia since heart block in patients who are anemic and/or febrile may be overlooked on physical examination.

REFERENCES

1. ARONSON, S. F. and LEROY, E. Electrocardiographic findings in leukemia. *J. Hematology*, 2: 356, 1947.
2. BLOTNER, H. and SOSMAN, M. C. X-ray therapy of the heart in a patient with leukemia, heart block and hypertension. *New England J. Med.*, 230: 793, 1944.
3. KIRSHBAUM, J. D. and PREUSS, F. S. Leukemia, clinical and pathologic study of 123 fatal cases in a series of 14,400 necropsies. *Arch. Int. Med.*, 71: 777, 1943.
4. FORKNER, C. E. Leukemia and Allied Disorders. Pp. 97 and 333. New York, 1938.
5. WINTROBE, M. M. Clinical Hematology. 2nd ed., p. 683. Philadelphia, 1946. Lea and Febiger.

Book Review

The Acute Bacterial Diseases—Their Diagnosis and Treatment. By Harry F. Dowling, M.D., with the collaboration of Lewis K. Sweet, M.D. and Harold L. Hirsh, M.D. P. 465. illustrated. Philadelphia, 1948. W. B. Saunders Company. Price \$6.50.

This new book presents a discussion of acute bacterial diseases "with the purpose of combining the new order of diagnosis and treatment with that which is worth while in the old order. It is intended as a practical guide for physicians and interested students."

The work is divided into four main sections: Part I comprises a brief outline of the general diagnostic features of acute bacterial infections, followed by an extended review of the nature, mode of action, indications for use and toxic effects of therapeutic agents, including serum, sulfonamides, penicillin and streptomycin. Parts II and III deal with individual diseases caused by cocci and bacilli. Part IV considers bacterial infections in which exotoxins are a major factor and closes with a short appendix in which methods are described for the assay of penicillin and streptomycin in body fluids and the determination of sulfonamide levels in blood and urine.

In general the subject matter is well presented but many sections, especially those dealing with the treatment of specific disease entities, appear to have been written some time ago without recent revision. The appraisal of the sulfonamide drugs is uncritical and proper emphasis is not placed on the marked differences in their bacteriostatic properties as, for example, between sulfanilamide and sulfadiazine. The schedules of treatment with penicillin recommended smaller doses than are usually employed at present and are definitely inadequate in some instances, notably in the initial therapy of subacute bacterial endocarditis. The oral administration of penicillin is also repeatedly advocated although this method is generally considered to be wasteful of penicillin and fraught with the dangers of variable destruction and absorption of the antibiotic.

Several errors were noted. The portion of the sulfonamides not bound to protein is stated to be inactive therapeutically.

Shock associated with infection is considered to be irreversible when it "has reached a severe stage, as evidenced especially by depression of the systolic and diastolic blood pressures." Influenza is included among the list of diseases to be differentiated in cases of long-standing fever. In addition to these lapses the reviewer takes issue with the authors regarding their views on the frequent development of resistance to penicillin by pneumococci and group A hemolytic streptococci. Moreover, the lurid description of the chronic stage of brucellosis is unsupported by specific references and resembles a dramatic account for the lay press rather than a considered opinion for the guidance of the physician and student.

These critical comments should not be constructed as impugning the value of the book as a whole. The authors are to be congratulated for a timely, concise, well planned account of their subject.

H.M.R.

It has been called to my attention that in the review entitled "Psychosomatic Medicine, Its History, Development and Teaching" by Dr. Bernard B. Raginsky of Montreal, Canada, which appeared in *The American Journal of Medicine*, in December, 1948, certain verbatim quotations were not properly acknowledged. These paragraphs on page 861, were taken from an article by Dr. Manuel D. Zane of New York entitled "Psychosomatic Considerations in Peptic Ulcers" which appeared in *Psychosomatic Medicine*, 9: 372-380, 1947.

The following statements are those in question:

"Most clinicians . . . accepted concepts in peptic ulcers."

"Many workers . . . consider as insurmountable."

"Although the underlying conflict . . . unobtrusive."

"In 1932 Cushing . . . pepsin-bearing glandular tissue."

"This concept affords . . . effective approach to them."

The editor regrets this oversight, which appears to have been unintentional, and offers his apologies to Dr. Zane and to the editors of "Psychosomatic Medicine."

ALEXANDER B. GUTMAN, M.D.

Foreword

THERE have been many and various symposia on poliomyelitis and perhaps there is nothing unique about this one which might serve to distinguish it from those which have gone before. However, there are points about this series of articles which it would be a mistake not to mention. Primarily they have been prepared for the *internist*, whether he or she is in general practice, special practice or engaged in "hospital medicine." This is the main objective; and if this series of articles can be said to have a central theme, it is the *medical aspect of the acute disease*—the virus infection of poliomyelitis. To supplement this central theme we have tried to include what precedes the acute disease and what follows it in relation to the natural history of poliomyelitis. For, no true clinical description of acute poliomyelitis, however concise, would be adequate today without ancillary considerations with regard to the epidemiology of the disease, its pathogenesis and pathology, its disturbances in physiology, its late management and at least brief mention of its public health aspects.

Some critics might inquire at the onset whether any new series of articles on poliomyelitis is worth reading in view of the claim that so much is written about poliomyelitis and there is so little that is new. With this latter assumption the articles in this symposium take issue. It is true that fundamental questions still remain to be answered, such as (1) How can acute poliomyelitis be cured or arrested? (2) How is poliomyelitis spread? (3) How can poliomyelitis be prevented? But the same can be

said of cancer, or certain forms of heart disease and, in fact, many common and important medical conditions. It is freely granted therefore that the answers to these three questions will not be found in these articles but other things will be found both timely and new, and some of these I would like to point out:

For instance, in developing current knowledge of the clinical picture of poliomyelitis Dr. Horstmann has emphasized that textbook descriptions of this disease have in the past been largely limited to the picture of the paralytic disease in infants. Recently there has been a relative shift in the age prevalence of poliomyelitis in this country and Europe and, although all are not agreed as to whether age-specific rates have changed, there is no question that in the average series of poliomyelitis patients which are now seen each summer in this country there is a greater percentage of cases among adolescents and young adults than there was a generation ago, a point which has also been made by Dr. Howe in his article on the epidemiology of this disease. Poliomyelitis in the adolescent or young adult has come to occupy a more important place than ever before. The pediatrician no longer dominates the field. Dr. Horstmann's current studies, based on the large epidemics of 1948 in North Carolina and California, indicate the manner in which adult poliomyelitis differs from old-fashioned "infantile paralysis." Absence of such knowledge in the past has caused confusion and difficulty in the diagnosis of poliomyelitis in adults.

Also, in developing current knowledge of the clinical picture of poliomyelitis Dr. Horstmann has indicated that the clinician cannot pass lightly over the abortive and non-paralytic cases of poliomyelitis even though their significance is trivial as far as a serious result to the patient is concerned. The line which separates the non-paralytic from the paralytic patient is very fine indeed. Thus an important responsibility on the part of the clinician is to protect non-paralytic patients from anything which may upset that delicate balance which determines whether or not the degree of central nervous system involvement will be sufficient to cause clinical paralysis.

Another feature is Dr. Baker's consideration of the most serious clinical form of poliomyelitis, namely, the bulbar form. Within the last three years, management of this type of case has been almost revolutionized.

The after-care of poliomyelitis and considerations with regard to physiotherapy and physical medicine, as well as the approach of the orthopedic surgeon, receives fewer pages in this series of articles than in other similar symposia. We could not cover all fields *in extenso*, particularly as we are concerned here with medical aspects of the *acute* disease. But the orthopedic approach and the technics of physical medicine have not been neglected, to which the articles on the use of moist heat by Dr. Green and the considerations of after-care by Dr. Bennett bear witness.

Some familiarity with the virus of poliomyelitis and its capacity to immunize is essential to the clinician. The lag in this knowledge has been due, in part, to a general lack of appreciation of the fact that

there are multiple strains of poliomyelitis virus. Today it is common knowledge that a small but definite family of poliomyelitis viruses exists, as indicated by Dr. Ward. Advances along these lines have been made in Dr. Isabel Morgan's laboratory, and in her article she has mentioned that repeated experimental infections with heterologous strains can be produced in the same animal. It is likely that this also occurs in man for second attacks of poliomyelitis in man might be due to re-infection with different strains of the virus. It would seem that if we are to project these findings forward with an eventual view to possible control of the human disease, the best chance for artificial immunization rests upon an appreciation that the immunizing agent or agents should perhaps be "polyvalent," or at least should have a broad antigenic component.

Another aspect with regard to pathogenesis or pathology is the concept of cerebral lesions in this disease, as developed by Dr. Bodian. The fact that the central nervous system lesions are so extensive, and not limited to the anterior horn cells of the spinal cord, raises considerations as to whether some of the symptoms which have been interpreted by clinicians in the past on the basis of anterior horn cell lesions are not actually due to brain stem or cerebral lesions. Dr. Bodian indicates that as far as the pathologist is concerned all cases of poliomyelitis are 'encephalitic.'

And finally it is a pleasure to have this series as a medium in which Dr. Buchtal of Copenhagen, Denmark again can present the distinguished work of his Neurophysiological Institute to American readers.

JOHN R. PAUL, M.D.
Yale University School
of Medicine

Symposium on Poliomyelitis

Epidemiology of Poliomyelitis in the Light of Modern Research*

HOWARD A. HOWE, M.D.

Baltimore, Maryland

ALTHOUGH poliomyelitis was first described by Heine in 1840,¹ it apparently was not recognized as an epidemic disease until much later in the century. The first sizable outbreak to be noted took place in Stockholm in 1887 and comprised forty-four cases. (Medin 1891.)² The many reports of scattered cases during this hiatus show with little doubt, however, that the disease was constantly present in western Europe. A similar trend can also be seen in the United States. Colmer in 1843³ described "teething paralysis," a malady which he found confined to a small group of children under two years of age in Louisiana. This was followed in 1894 by Caverly's account of an epidemic comprising 132 cases of undoubted poliomyelitis in Vermont.⁴ In Sweden the year 1905 marked the first of a series of large epidemics of poliomyelitis which were to plague the people of the temperate zones from that time to the present. Wickman's description⁵ of this Swedish epidemic (1,031 cases) established the epidemiologic pattern of poliomyelitis and thinking about it has varied little since that time although additional documentation has been produced to support numerous points which were deduced by Wickman on epidemiologic evidence alone.

Wickman characterized poliomyelitis as an epidemic infectious disease affecting children primarily and spread by contact with clinical and subclinical cases or symptomless carriers. He was able to describe many secondary cases apparently

resulting from contact with infected individuals, in all probability because the epidemic involved small villages and rural areas which could be intensively studied. This experience has been duplicated in more recent times in other areas, both rural^{6,7} and urban.^{8,9} The precise type of contact was not known to Wickman nor is it known today.

In 1912 Kling, Petterson, Wernstedt and Josefson¹⁰ found virus in throat washings and intestinal contents from fatal paralytic and non-paralytic patients. While somewhat questionable from a laboratory standpoint, these findings have been amply confirmed in more recent times.¹¹⁻¹⁶ The discovery of a dual mechanism by which virus might escape from the infected individual unfortunately could not settle the question of the mode of transmission of poliomyelitis nor has the more recent finding of virus in association with flies and urban sewage¹⁷⁻¹⁹ contributed crucial evidence. For some years these basic observations have been shuffled in different proportions into various combinations, some with modern trimmings and with changing emphasis on the means by which virus may reach the susceptible human host. This may never be exactly demonstrated. Nevertheless, recent research has done much to indicate what must be known about poliomyelitis in order to break the chain of transmission at its most accessible point.

Wickman believed that his evidence implicated man as the source of the virus and modern work has done little to refute

* From The Poliomyelitis Research Center, Department of Epidemiology, Johns Hopkins University, Baltimore, Md.
Aided by a grant from The National Foundation for Infantile Paralysis, Inc.

this conclusion. No true animal or plant reservoir has yet been demonstrated²⁰ since even the virus, which is found in association with flies, appears to be of human origin rather than the result of growth within the insect itself.²¹ Such being the case, it is logical to look within man's rather immediate environment for the conditions which allow an equilibrium between the host and the parasite. It is therefore necessary to think not only in terms of the degree of man's exposure to the virus but also his reaction to previous exposure, that is, his immunity.

It can be shown in a number of ways that humans become solidly immune to paralysis by poliomyelitis virus although this statement requires some qualification in relation to different virus types which will be made later in this paper. Furthermore, monkeys paralyzed by inoculation of poliomyelitis virus do not become paralyzed again upon re-inoculation of the same material,²² nor would poliomyelitis continue to be a children's disease except under very special conditions of exposure unless the presence of widespread immunity were the explanation. Thus while the apparent predilection of the disease for children has several interpretations only one seems in conformity with the facts. It is not logical to assume that exposure to the virus is significantly greater in the younger age groups since all ages live in the same homes. Neither can it be shown that mere physiologic maturity brings a type of non-specific resistance for the average age of paralytic patients has been consistently higher in rural areas than in large cities of the same climatic zone.²³⁻²⁵ The exclusion of these possibilities leaves the acquisition of specific immunity as the most acceptable explanation of the age selection in poliomyelitis. This is corroborated by the fact that the acquisition of serum antibody against the Lansing type of poliomyelitis virus closely follows the age pattern of the paralytic disease²⁶⁻²⁸ and that the distribution of antibody to an unclassified virus type in urban and rural areas is also in conformity

with the age distribution of the overt disease.²⁹

It is generally recognized that many poliomyelitic infections produce no symptoms at all, or that they may be associated with a non-specific syndrome consisting of fever, malaise, headache, nausea, vomiting, constipation or sore throat in various combinations.³⁰ These cannot with assurance be recognized as poliomyelitic infections even in the presence of an epidemic setting without virus isolation. Patients who present muscle pains and stiff neck or back in addition to the previously mentioned signs and symptoms, and who also show an increase in leukocytes and protein in the spinal fluid as an indication of CNS involvement, may be diagnosed as having non-paralytic poliomyelitis with more assurance, particularly if these symptoms occur in association with paralysis. However, the distinction of these non-paralytic patients from those showing weakness and paralysis of voluntary muscle is entirely one of degree since in both types the CNS is invaded.³¹

One can get some idea of the relative numbers of clinically recognizable and subclinical cases by a comparison of poliomyelitis and measles, diseases which, for the most part, reach the individual before the twenty-fifth year of life. In Baltimore between 1921 and 1944, 119,432 cases of measles were reported among the white population while during the same period only 898 cases of paralytic poliomyelitis were recorded. (Table 1.) Similarly, in the rest of the state of Maryland, exclusive of Baltimore, from 1920-1945 the records show 97,909 cases of measles in all races and 1,185 cases of paralytic poliomyelitis with virtually the same age distribution. It is difficult to escape the conclusion that there were during this period an average of one hundred poliomyelitic infections to one reported case.

Approximately the same ratio of clinical to subclinical cases is indicated by the survey of Selwyn Collins³² which included 20,258 individuals from zero to twenty-four

years of age in twenty-eight cities of the United States. In this group 11.01 per 1,000 had a history of antecedent poliomyelitis, including death. Since poliomyelitis incidence is negligible over twenty-five years of age, these figures indicate that effective

During that time the largest reported outbreak consisted of eleven cases, producing a "rate" of roughly 37 per 100,000 persons which is equivalent to those reported in Baltimore at epidemic times. Easton and its environs were conscious of poliomyelitis but

TABLE I
REPORTED CASES OF MEASLES AND POLIOMYELITIS BY AGE GROUPS—COUNTIES OF MARYLAND, 1916-1943

Age Groups	Cases of Measles			Cases of Poliomyelitis		
	As Re-reported	Accumulated by Age		As Re-reported	Accumulated by Age	
		No.	Per Cent		No.	Per Cent
0-4	24,128	24.3	614	51.7
5-9	43,087	67,215	67.8	282	896	75.6
10-14	16,365	83,580	84.3	157	1,053	88.9
15-19	6,772	90,352	91.2	69	1,122	94.7
20-39	7,109	97,461	98.4	53	1,175	99.1
40-59	708	98,169	99.1	5	1,180	99.6
60+	95	98,264	99.2			
Unknown	815	0.7	5	0.4
Total:	99,079	99,079	100.0	1,185	1,185	100.0

* Figures obtained through the courtesy of Dr. Riley of the Maryland State Dept. of Health.

immunity had been achieved by the population at the rate of approximately one hundred infections to one clinically recognized case. A similar ratio has also been arrived at by Casey and his co-workers on the basis of clinical-epidemiologic observations.³³

Another picture of the subclinical immunization process may be seen by comparing the reported cases of poliomyelitis over a period of twenty-five years in a large city such as Baltimore with two smaller cities of Maryland. (Table II.) While the disease has been reported every year in Baltimore with periodic upswings, the smaller cities of Hagerstown and Easton have had a much less spectacular, although typical, experience with poliomyelitis.

In Hagerstown and its rural districts poliomyelitis has been reported only half of the years from 1925 to 1948, inclusive.

TABLE II
REPORTED CASES OF POLIOMYELITIS IN MARYLAND

	Baltimore (white patients only). 1940 White Population 693,257	Hagerstown and Rural District. 1940 Population 32,491	Easton and Rural District. 1940 Population 4,528
1925	21*	2†	0†
1926	26	0	0
1927	9	0	0
1928	122	1	0
1929	9	0	0
1930	19	3	1
1931	13	1	0
1932	13	0	0
1933	13	0	0
1934	10	0	0
1935	46	0	0
1936	6	11	0
1937	45	0	0
1938	2	0	0
1939	10	0	1
1940	4	0	0
1941	90	2	2
1942	3	1	0
1943	7	1	0
1944	152	5	0
1945	21	2	0
1946	25	0	0
1947	26	3	1
1948	13	2	0

* Figures from the Baltimore City Health Dept. (courtesy of Dr. Fales).

† Figures from the Maryland State Health Dept. (courtesy of Dr. Riley).

four times during this twenty-three-year period. In 1941 two cases were reported, producing a rate of 58/100,000. No one can doubt that poliomyelitis was present more frequently and extensively than is indicated by these "epidemics," and that the populations of these towns were being immunized with only slightly less thoroughness than those of Baltimore. The consistent selection of children under twelve years (100 per cent in Easton and 70 per cent in Hagerstown) is the best proof of this.

It is important, however, to emphasize that while these estimates probably reflect the over-all picture they may be in error for any given situation. For example, it is generally accepted that certain virus strains consistently produce severe paralysis in laboratory animals while others may be associated with such mild disease that microscopic examination is necessary in many cases to establish the existence of infection. There is every reason to believe that these same differences occur in nature. Since the recognition of a poliomyelitis epidemic depends primarily on the identification of cases, it is clear that a number of variables will determine the extent of its recognition. These include not only the severity of the infection, as has been just suggested, but also the reporting practices and abilities of the attendant physicians, as well as the season and locality in which disease occurs and also the residence and age of the patients. These last variables may account for deficits in reporting as high as 68 per cent, even in a poliomyelitis-conscious community (the state of Massachusetts) where small town physicians are particularly loath to make a diagnosis of poliomyelitis in an infant during the winter months of a non-epidemic year.³⁴ It is not surprising, therefore, to encounter numerous inconsistencies in the reported incidence of poliomyelitis.

Modern laboratory studies have shown the virus of poliomyelitis to be present in stools during the acute stages of the paralytic disease in such a high percentage of cases that it seems justifiable to consider it a constant concomitant of CNS invasion.^{35,36} This probably is true for non-paralytic patients although the documentation is not extensive. Within a week of the onset of symptoms the frequency with which virus can be demonstrated in stools falls off but, nevertheless, virus has been shown to persist in some individuals for as long as eleven to twelve weeks.^{13,37,38}

Virus has also been demonstrated in swabs taken from the throats of acute paralytic patients and in face masks worn

by juvenile patients who had coughed and drooled into them.³⁹ While virus has been isolated from the throat¹⁴⁻¹⁶ in nearly 50 per cent of the patients within three to five days of the acute onset of disease, its incidence falls off very rapidly thereafter. Occasional isolations from abortive cases are recorded as late as the eleventh day.¹⁶ It is probable that the failure to detect virus in the oropharynx as long as in the stools reflects a real biologic difference since it is known that antibody may be present in the pharyngeal secretions,⁴⁰ although it has not been demonstrated in the stools. It is therefore possible that the antibody response following infection clears the pharynx of virus in a relatively short time.

Little is known about the incidence of virus in the stools or pharyngeal secretions prior to the onset of symptoms although it has been described in the former twelve and nineteen days before onset.^{41,42} There have also been a few isolations of virus from the oropharynx four to six days before clinical symptoms were observed.^{43,44} Investigation of the virus distribution in the family associates of a patient has amply demonstrated the relative frequency of asymptomatic virus infections of the alimentary tract⁴⁵⁻⁴⁷ while random sampling of the population at epidemic times has suggested a wide distribution of oropharyngeal and fecal virus carriers⁴⁸⁻⁵⁰ many of whom were not sick. Pearson et al.,⁴⁶ in a survey of infected individuals in the Fort Worth, Texas poliomyelitis epidemic of 1943, have provided the data from which to compare the number of observed subclinical infections with that expected if the ratio of clinical to subclinical infection were approximately 100 to 1. For example, during the period of their study ten cases of reportable poliomyelitis occurred in a city of 200,000 persons. If in reality 1,000 infections had developed during this period, one would have expected an infection rate of .005. The investigators drew a sample of 374 persons who had no known history of contact with a patient with poliomyelitis. On the basis of the aforementioned rate 1.8

silent infections would have been expected in this group and at least two were found.

Modern studies have effectively ruled out the olfactory mucosa as a portal of entry of the virus by the demonstration that the olfactory bulbs of fatal human patients do not show characteristic lesions^{51,52} or contain virus.⁵³ Nor is there evidence that the virus proliferates in the olfactory mucosa⁵³ although it is easily found in the pharynx and contents of the gut of both patients and carriers. Although it is not entirely clear how the virus gains entrance to the alimentary tract, the evidence points strongly to it as the tissue from which invasion of the CNS takes place. There is a large body of fact indicating that the virus travels by way of nerves to the CNS and is disseminated within it along nerve pathways.¹⁰⁵

Poliomyelitis might be transmitted from one individual to another in a variety of ways: indirectly by an arthropod vector with or without an animal reservoir, through mass contamination of food or fluid by feces, relatively directly by hand-to-mouth transfer of feces or pharyngeal secretions from child to child or through playthings, finally, by immediate droplet ("respiratory") contact.

The first possibility, that of a blood-sucking arthropod with or without an animal reservoir, may be ruled out with reasonable assurance. Since poliomyelitis does not have an important blood stream phase,⁵⁴ there is little reason to expect that blood-sucking insects would become infected from man. Furthermore, it is difficult to visualize either an animal reservoir or an arthropod vector of sufficiently universal distribution to account for the world-wide extent of poliomyelitis. Also, the diffuse pattern of poliomyelitis in city and country is quite different from the rural concentration of St. Louis encephalitis and equine encephalomyelitis, both mosquito-borne, as well as the special localizations of arthropod-transmitted rickettsial disease.⁵⁵ Furthermore, the persistence of poliomyelitis epidemics into the winter months clearly differentiates this disease from mosquito-

transmitted equine encephalomyelitis which ceases abruptly with the advent of cold weather.⁵⁶

Spinal cord emulsions containing Lansing virus are rapidly inactivated by sludge.⁵⁷ Nevertheless, since it is known that active virus is discharged by certain sewage plants into streams, contaminated water is a potential source of infection. While there is some difficulty in translating the results of laboratory experiments to the conditions of urban water disinfection,^{58,59} it appears that ordinary methods for the purification of drinking water are effective. Even if this were not true, however, the slow radial spread of poliomyelitis from a circumscribed focus is not that of an explosive epidemic disseminated through a city water distribution system.^{7,60} It is impossible to consider drinking water as the agent for dissemination of the disease in rural districts where each family usually has an individual water supply unless one thinks of the entire water table of an area as contaminated.

Mass contamination of a single source of milk has been reasonably indicated in only three epidemics despite diligent search so that it seems likely that mass contamination of food would not go unnoticed.⁶¹⁻⁶³ The fact that there are frequently multiple cases occurring in families within a few days suggests a common exposure. Lavinder, Freeman and Frost⁶⁰ found 70 per cent of multiple familial poliomyelitis cases occurring within five days and but 40 per cent of diphtheria or scarlet fever cases so distributed. Aycock and Eaton⁶⁴ suggested that this phenomenon could be explained by the advent of an asymptomatic carrier into a household. However, it is also consistent with the idea of contamination of food by flies.

In a very ingenious experiment Ward, Melnick and Horstmann⁶⁵ exposed bananas and fly bait to flies for twenty-four to forty-eight hours on the back porches of some twenty rural homes in which there was poliomyelitis. When the material was fed to two chimpanzees, both developed inapparent poliomyelitic infections. Unfortu-

nately, the food was to some extent also exposed to the general environment as well as to the flies so that this important control is not entirely satisfactory, but there seems to be little reason to doubt that a large number of infected flies could contaminate food if allowed access to it for considerable time.

It is difficult to assess the role of flies in the usual spread of infection. Experiments on fly abatement with D.D.T. have not resulted in any demonstrable control of epidemics but have almost invariably been instituted while the epidemic was at its peak or on the decline.⁶⁶

Another episode which appears to minimize the importance of flies took place in connection with an unprecedented poliomyelitis outbreak on the Island of Malta where human sewage is used to fertilize the fields. During August and September the incidence of typhoid rose but the outbreak of poliomyelitis did not occur until December and January when there were virtually no flies present.⁶⁷ It may also be valuable to cite an outbreak of poliomyelitis at Elkins, West Virginia involving seventy cases which took place entirely in the winter.⁶⁸ The temperature was below freezing most of the time and flies were seen only occasionally on unusually warm days.

For the most part, infected flies have been trapped in rural areas where they had ready access to human feces,⁶⁹ but infected catches have also been made in cities with modern sewage disposal such as Cleveland, Ohio⁷⁰ and Rockford, Illinois.⁷¹ Despite these findings urban fly populations in general have declined greatly since the advent of the automobile, with a concomitant decrease in dysentery rates but without any corresponding decrease in the incidence of poliomyelitis. The role of the fly then remains an indeterminate one since no positive evidence for its participation has been advanced to counter such negative evidence as the aforementioned.

While it was claimed in 1911 that poliomyelitis virus had been isolated from the dust of a sick room,⁷² confirmation of this

observation with modern methods has not come to light, nor is it known how long virus remains active when dried in fecal remnants or droplet nuclei. While virus might retain its activity for some hours on inanimate objects, it is not necessary to postulate a longer survival time to account for the transmission of the disease.

The evidence for direct person to person transfer of virus is again largely circumstantial. However, no one who has watched children at play can doubt that many opportunities exist for the transfer of pharyngeal secretions or feces, not only among the children themselves but also to their adult associates. Two independent epidemiologic studies based upon secondary cases presumably arising from a single contact with an extrafamilial primary case^{6,73} both indicate the infectious period to be four to five days before and after the onset of symptoms. This interval, of course, corresponds very closely to that during which virus is readily demonstrable in the pharyngeal secretions of the patient. The fact that the continued elimination of virus in the stools has not been connected with appearance of secondary cases again constitutes negative evidence in favor of spread through pharyngeal secretions. Both poliomyelitis and measles spread radially and appear to be equally infectious^{7,74} yet patients with poliomyelitis do not have the cough or coryza which is characteristic of measles. It must be recognized, however, that some children emit visible mouth spray even in ordinary conversation. Since the minimal infective dose of virus probably is very small and the virus might at some times be present in saliva, this type of direct contact is at least possible. It has received little attention by modern workers. The absence of lesions in the olfactory bulbs of man does not necessarily rule out airborne infection. This simply may be an expression of the experimentally observed fact that the nasal mucosa is not a tissue in which the virus proliferates as readily as in the oropharynx.

Since the carrier state may be transient,

the demonstration of infection in all the members of a family at the time of its occurrence^{16,45-47} does not prove that all of the individuals were infected by a common exposure unless it can be shown that all were free of virus on more than one occasion during a period of five to twenty-one days previous to the onset of the disease.

Although it appears that much of the evidence favors the idea that poliomyelitis is transmitted through pharyngeal secretions, the suggestive power of analogy is so strong that it is very difficult to avoid falling in with the idea that a disease with a summer epidemicity is invariably enteric. The possibility still exists that there is a dual mechanism involved and that fecal contamination, both through the agency of flies or by more direct transfers, may operate under certain conditions. This point of view recently has been presented and ably supported by Sabin.⁷⁵ It has been suggested, furthermore, that flies may be responsible for the initiation of summer outbreaks which then continue by person to person contact.⁶⁵

While poliomyelitis was recognized as an epidemic disease in the north temperate zone just before the turn of the century, it is still essentially endemic in character in such places as Malta,⁶⁷ El Salvador,⁷⁶ Puerto Rico,⁷⁷ Venezuela,⁷⁸ Ecuador⁷⁹ and Palestine⁸⁰ where, with the exception of Malta, only small outbreaks have been noted in recent years. In these epidemics, as in the first ones to be recorded in north Europe and the United States, 80 to 90 per cent of the cases occurred in children under five years of age. While doubtless only the severe paralytic cases have been recognized, the remarkable correspondence of age selection in all of these areas can scarcely be laid to ignorance of paralytic poliomyelitis in older children or in adults. It seems probable that lack of recognition of the disease would create less distortion in the pattern of age selection than in that of total incidence. It is certainly difficult to explain the apparent absence of large epidemics in relatively primitive countries on the basis of the continued presence of mild virus strains since

during World War II British and American troops contracted paralytic and even fatal disease while stationed in areas where poliomyelitis was virtually unknown in the native populations.^{67,81-83} Obviously, then, one can say relatively little about the

TABLE III
AGE SPECIFIC MORBIDITY RATES—ADJUSTED TO TOTAL RATE
FOR 1920-1924 (MODIFIED FROM DAUER)

Year	Age Groups				Factor
	0-4	5-9	10-19	20+	
1920-24	32.5*	14.9	7.9	1.4	1.000
1925-29	22.6	15.1	6.4	0.80	0.6715
1930-34	22.6	20.3	7.8	0.81	0.4517
1935-39	20.6	23.3	9.1	0.76	0.7582
1940-44	14.9	22.4	9.5	0.93	0.5476

AGE SPECIFIC POLIOMYELITIS MORTALITY RATES—ADJUSTED
TO TOTAL RATE FOR 1920-1924

Year	0-4	5-9	10-19	20+	Factor
1920-24	5.3*	2.7	1.6	0.34	1.000
1925-29	3.9	3.1	1.9	0.34	0.9041
1930-34	3.6	3.9	2.3	0.47	1.0645
1935-39	3.6	4.1	2.5	0.64	2.2758
1940-44	1.4	3.8	3.0	0.64	2.000

* Average annual rates per 100,000 persons.

character of poliomyelitis in primitive countries beyond noting that the disease is clearly world-wide in its distribution.

Since the recognition of poliomyelitis as an epidemic disease, further modifications in age selection have taken place which in all probability reflect both the past and present experience of the population with the virus. For example, in the United States there has been a consistent reduction in the age specific rates for children under five years. This has been noted in relation to deaths since 1910 for the registration area of that time by Gilliam,⁸⁴ and since 1920 in relation to total reported cases as well as deaths in five northern states by Dauer⁸⁵ whose figures are presented in Table III and Fig. 1. Both authors agree that there has been a progressive decrease in total death rates although considerable variability is encountered from year to year because of local factors. In order to empha-

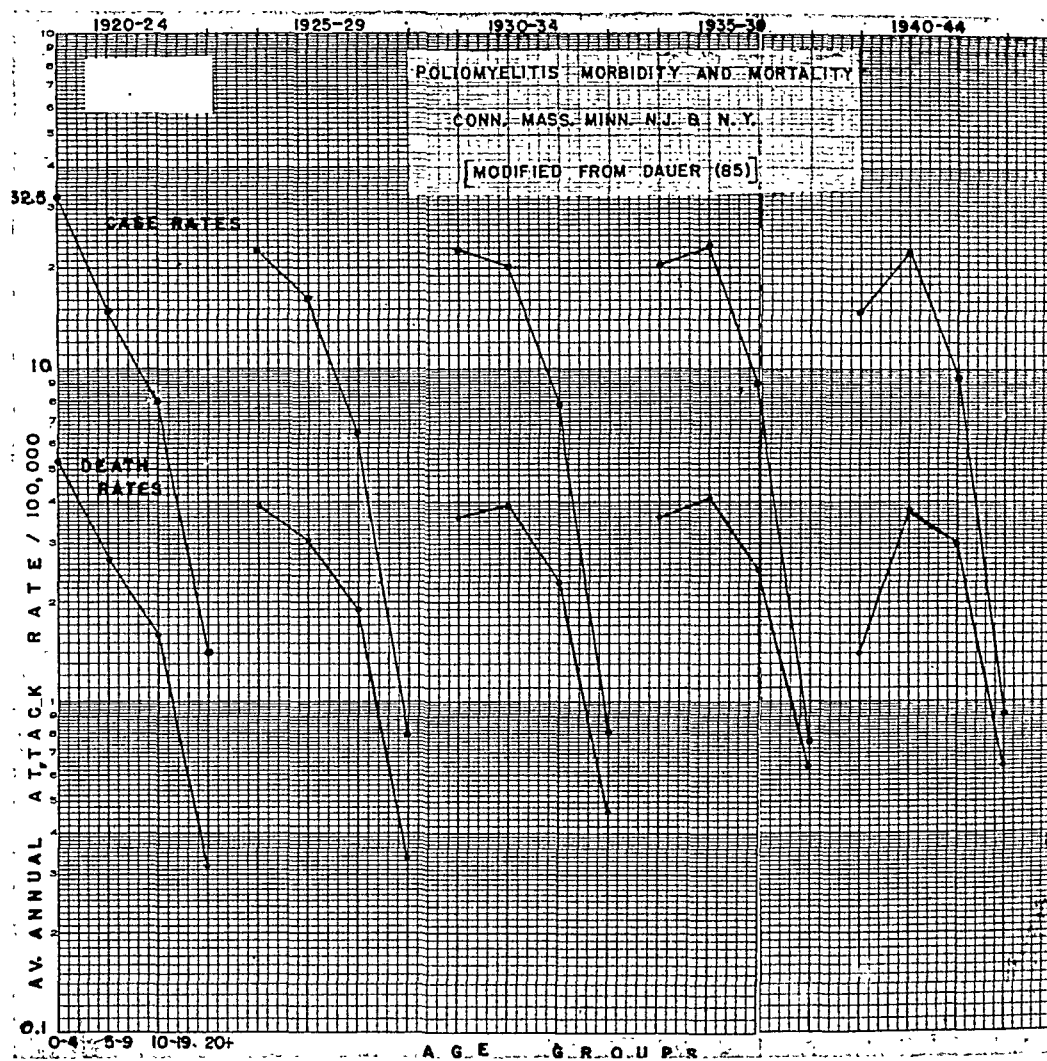


FIG. 1

size the age trends the average five-year rates for the age groups have been multiplied by a factor representing the relative decrease or increase in the total rate since 1920 to 1924 (last column in Table III). When this is done, the relative shifts in age selection are clearly visualized. It can be seen that the striking decrease in deaths under five years has apparently been balanced by a rather uniformly distributed increase in all the older groups.

Total reported cases (paralytic and non-paralytic) show the same trends although the relative drop in the rates under five years is less spectacular than that observed in the death rates. Here there has been a definitely greater incidence in the five to nine-year group so that the slope of the first

limb of the curve has changed because of alterations at both ends. While there is a slight relative increase in the ten to nineteen-year class, this limb of the curve has scarcely altered its slope, indicating that changes in this group relative to the five to nine-year group have been proportional. Such a small increase has taken place in the selection of adults that there is scarcely any perceptible alteration in the slope of this portion of the curve.

Essentially the same findings have been reported since 1911 for Denmark and Sweden^{86,87} where deaths and paralytic cases have been tabulated separately, thus avoiding admixture of an unknown number of non-paralytic patients who do not have the same age distribution as the paralytic

ones.⁸⁷⁻⁸⁹ In the Scandinavian countries there has been the same relative reduction of incidence under five years of age but a considerably more marked selection of adults than is indicated by the American statistics. The shift toward older ages, however, is by no means as striking as one is led to believe from tabulations dealing only with the per cent age distribution of patients, a measure which is distorted by the marked aging of the population.

It is impossible on the basis of present knowledge to do more than suggest several possible explanations for this phenomenon. Burnet⁹⁰ has advanced the hypothesis that mutation of the virus has resulted in strains which produce a higher percentage of paralytic infections. While mutation of the Lansing type has been known to take place under drastic experimental conditions, there is thus far no crucial evidence that this has happened in nature nor is it clear that the actual incidence of paralytic disease has greatly increased. Dauer⁸⁵ suggests that much of the apparent trend in the last twenty years may be due to improved criteria for diagnosis and more complete reporting.

The decrease in the size of families must also be considered in this connection. If the virus is introduced into the family by older children, it is obvious that a child without older siblings has less opportunity of meeting the virus in infancy than the child who is a young member of a large family. In this case, however, one would expect a shift in the age incidence of other childhood diseases. The experience of Baltimore in this regard is of interest although it may not be typical. The population has been aging since 1920 and, concomitantly, there has been a shift of maximal paralytic poliomyelitis incidence from the zero to four to the five to nine-year group. At the same time, however, there has been no comparable change for measles and whooping cough. This suggests that the epidemiology of the latter two diseases is different from that of poliomyelitis, also that they have reached a stable equilibrium with the

population which is not easily upset while such is not the case for poliomyelitis. (Fig. 2.)

Selwyn Collins' study³² has shown the age shift to be greater in the group with an income above \$3,000. This suggests that the better class home is not so heavily seeded with virus as in the past. This would be equally true whether the virus were introduced by the school age child or whether it had become less prevalent in the home because of reduced exposure of food, etc. to flies or because of other sanitary improvements. In the countries which have shown changes in age selection the past generation has seen marked alteration not only in general sanitation but also an improvement of diet and the degree of housing congestion. These changes, perhaps collectively, have been accompanied by striking reductions in the incidence of enteric diseases such as typhoid and dysentery. Meanwhile, little has happened to poliomyelitis beyond the shift in its age selection which has just been discussed.

The demonstration of at least three immunogenically different types of poliomyelitis virus⁹¹⁻⁹³ offers the possibility of clarifying considerably the irregularities in epidemic pattern which are encountered from time to time⁹⁴ even though there may be considerably more cross immunity following natural infection than has been demonstrated in artificially immunized laboratory animals.²² It is also of more than passing interest that strains of virus which are immunogenically indistinguishable nevertheless differ markedly as regards their clinical properties in laboratory primates, some being very mild and others producing extensive paralysis.^{93,95} The possibility, therefore, exists for a succession or a mixture of types in various times and areas. It may not be irrelevant in this connection that strains representing the three presently known types have all been isolated from the Los Angeles area since 1934. Two of these produce very severe disease in monkeys while the third is very mild.

While it is highly probable that more

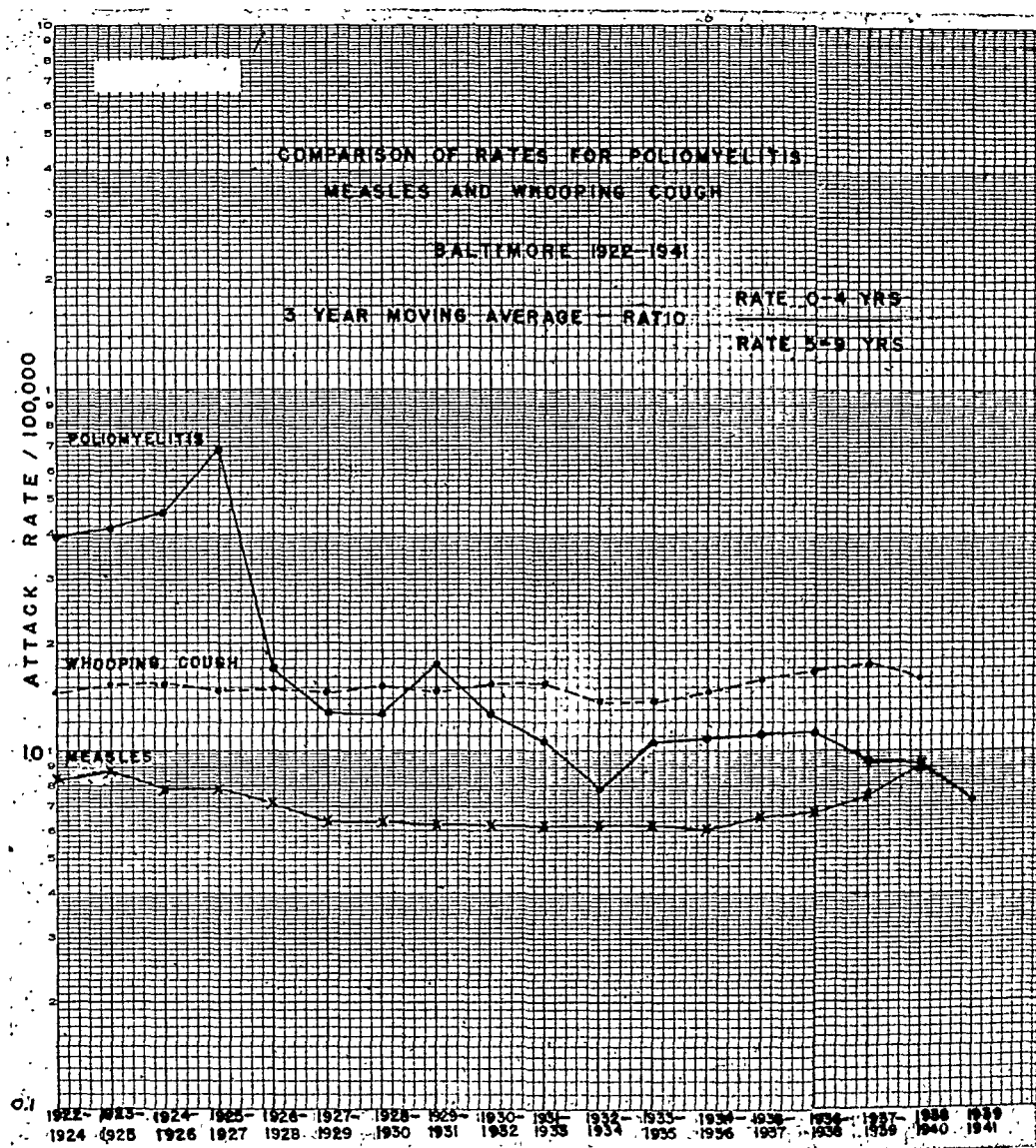


FIG. 2

than three types of virus exist, the number cannot be large else poliomyelitis would not be primarily a children's disease. The fact that well authenticated second attacks of poliomyelitis occur in no way abrogates the interpretation that adult immunity is the result of specific experience with various virus types. Second paralytic attacks may be induced in the laboratory with heterotypic virus types but it is significant that even under these extreme conditions paralytic rates are much lower than those observed in animals which have had no previous experience with poliomyelitis virus.²² Several studies in recent years⁹⁶⁻⁹⁸

have purported to show that attack rates for the entire susceptible population in a given epidemic are of the same order of magnitude as those for second attacks. This is interpreted to indicate a complete absence of immunity following the first paralytic attack. Leaving aside the small numbers of second attacks and the questionable procedure of accumulating the paralytic cases over a period of nearly a generation as a denominator for calculating the rate of second attacks, a serious difficulty remains. Paralysis is an exceptional outcome of poliomyelitic infection and is suspected to be a function of genetic constitution.^{99,100}

In measuring second paralytic attacks one is therefore measuring a special event in a group already selected by the previous occurrence of this event—the risk of paralysis in a group of persons already shown to be especially susceptible to paralysis. This interpretation was, in fact, suggested by one group which participated in a study of second attacks.⁹⁷

Attempts at the control of poliomyelitis must be based upon a realistic interpretation of its epidemiologic characteristics. Since the ratio of unrecognized to recognized infection is of the order of 100/1, no widespread effect can be expected from the isolation of the patient and his immediate contacts, even though it has been shown that these represent an appreciable number of infected individuals. At best, one could look forward to preventing a few cases of infection (no one would willfully condone association with a patient or his family) but could not expect any appreciable effect upon an entire epidemic. While swimming pools are certainly a potential source of contagion, they have never been clearly implicated in the actual spread of the disease.

It seems inadvisable to hamper the life of an entire community for an objective which cannot be attained and which, if successful, would only delay to a less favorable age^{55,101} a natural immunization process which goes on at the rate of one casualty in one hundred infections. While it may be necessary to do something to maintain community morale, the physician who has no illusions regarding the effectiveness of "control measures" can keep them at a minimum. Quarantine has clearly not eliminated epidemics of measles, a disease in which virtually every infected individual and many of his contacts can be identified and eventually isolated.

The logical point at which to break the chain of infections is not by attempting to reduce exposure but rather to control infection by increasing immunity. While vaccines are still in the experimental stages, it is, nevertheless, possible to produce

immunity to intracerebral challenge with inactivated virus in both monkeys¹⁰² and mice.¹⁰⁴ The future of vaccine prophylaxis lies in increasing the knowledge of the number of virus types and their immunogenic relationships as well as by improvement in the methods of inactivating virus.

REFERENCES

1. HEINE, J. Beobachtungen über Lähmungszustände der unteren Extremitäten und deren Behandlung. (Observations on paralytic conditions of the lower extremities and their treatment.) Stuttgart, Köhler, 1840.
2. MEDIAN, O. Ueber eine Epidemie von spinaler Kinderlähmung. *Verhandl. d. X. internat. med. Kongr.*, 2: 6, 1890; 37-46, 1891.
3. COLMER, G. Paralysis in teething children. *Am. J. M. Sc.*, 5: 248, 1843.
4. CAVERLY, C. S. Infantile Paralysis in Vermont. Vermont State Department of Public Health, 1924.
5. WICKMAN, I. Acute Poliomyelitis. Nervous and Mental Disease Monograph Series 16. New York, 1913.
6. CASEY, A. E. Observations on an epidemic of poliomyelitis. *Science*, 95: 359-360, 1942.
7. PERKINS, J. E. Epidemiology of poliomyelitis. *New York State J. Med.*, 45: 159-168, 1945.
8. PISZCZEK, E. A., SHAUGHNESSY, H. J., ZICHIS, J. and LEVINSON, S. O. Acute anterior poliomyelitis; study of an outbreak in West Suburban Cook County, Ill.: preliminary report. *J. A. M. A.*, 117: 1962-1965, 1941.
9. CASEY, A. E., FISHBEIN, W. I. and BUNDESEN, H. N. Transmission of poliomyelitis by patient to patient contact. *J. A. M. A.*, 129: 1141-1145, 1945.
10. KLING, C., PETERSSON, A., WERNSTEDT, W. and JOSEFSON, A. Investigations on Epidemic Infantile Paralysis. Report from State Medical Institute of Sweden to xv. Int. Cong. on Hyg. and Demography, Washington. Upsala, Almqvist and Wiksells, 1912.
11. TRASK, J. D., VIGNEC, A. J. and PAUL, J. R. Poliomyelitis virus in human stools. *J. A. M. A.*, 111: 6-11, 1938.
12. HOWE, H. A. and BODIAN, D. The efficiency of intranasal inoculation as a means of recovering poliomyelitis virus from stools. *Am. J. Hyg.*, 40: 224-226, 1944.
13. HORSTMANN, D. M., WARD, R. and MELNICK, J. L. The isolation of poliomyelitis virus from human extra-neural sources. III. Persistence of virus in stools after acute infection. *J. Clin. Investigation*, 25: 275-277, 1946.
14. HOWE, H. A., BODIAN, D. and WENNER, H. A. Further observations on the presence of poliomyelitis virus in the human oropharynx. *Bull. Johns Hopkins Hosp.*, 76: 19-24, 1945.
15. WENNER, H. A. and TANNER, W. A. Poliomyelitis in families attacked by the disease. I. Distribution of virus in stool and oropharynx of members in households. *Am. J. M. Sc.*, 216: 258-269, 1948.

16. PEARSON, H. E. and BROWN, G. C. Recovery of virus from throats of poliomyelitis patients. *Proc. Soc. Exper. Biol. & Med.*, 66: 503-505, 1947.
17. PAUL, J. R., TRASK, J. D., BISHOP, M. B., MELNICK, J. L. and CASEY, A. E. The detection of poliomyelitis virus in flies. *Science*, 94: 395-396, 1941.
18. PAUL, J. R., TRASK, J. D. and CULOTTA, C. S. Poliomyelitic virus in sewage. *Science*, 90: 258-259, 1939.
19. MELNICK, J. L. Poliomyelitis in urban sewage in epidemic and in nonepidemic times. *Am. J. Hyg.*, 45: 240-253, 1947.
20. FRANCIS, T., JR., BROWN, G. C. and PENNER, L. R. Search for extrahuman sources of poliomyelitis virus. *J. A. M. A.*, 136: 1088-1092, 1948.
21. MELNICK, J. L. and PENNER, L. R. Experimental infection of flies with human poliomyelitis virus. *Proc. Soc. Exper. Biol. & Med.*, 65: 342-346, 1947.
22. BODIAN, D. Differentiation of types of poliomyelitis viruses. I. Reinfection experiments in monkeys (second attacks). *Am. J. Hyg.*, 49: 200-224, 1949.
23. NICOLL, M., JR. The epidemic of poliomyelitis in New York State in 1916. *New York State J. Med.*, 17: 270-274, 1917.
24. OLDT, F. Poliomyelitis. The epidemic of 1927 in Ohio, its inception, progress and decline. Ohio Department of Health, Columbus, 1929.
25. OLIN, G. and HEINERTZ, N. O. Das Auftreten der Kinderlähmung in Schweden 1930-1939. *Ztschr. f. Hyg. u. Infektionskr.*, 125: 153-174, 1943.
26. HAAS, V. H. and ARMSTRONG, C. Immunity to the Lansing strain of poliomyelitis as revealed by the protection test in white mice. *Pub. Health Rep.*, 55: 1061-1068, 1940.
27. TURNER, T. B., YOUNG, L. E. and MAXWELL, E. S. The mouse-adapted Lansing strain of poliomyelitis virus. IV. Neutralizing antibodies in the serum of healthy children. *Am. J. Hyg.*, 42: 119-127, 1945.
28. PAIT, C. F., KESSEL, J. F. and GROSSMAN, P. The neutralization of the mouse-adapted poliomyelitis virus by the sera of patients, family contacts and normal children in Los Angeles. *Am. J. Hyg.*, 47: 335-344, 1948.
29. AYCOCK, W. L. and KRAMER, S. D. Immunity to poliomyelitis in normal individuals in urban and rural communities as indicated by the neutralization test. *J. Prev. Med.*, 4: 189-200, 1930.
30. CASEY, A. E., FISHBEIN, W. I., GORDON, F. B. and SCHABEL, F. M., JR. Clinical manifestations of infection with poliomyelitis virus. *J. A. M. A.*, 138: 865-868, 1948.
31. BODIAN, D. and HOWE, H. A. Non-paralytic poliomyelitis in the chimpanzee. *J. Exper. Med.*, 81: 255-274, 1945.
32. COLLINS, S. D. The incidence of poliomyelitis in its crippling effects, as recorded in family surveys. *Pub. Health Rep.*, 61: 327-355, 1946.
33. CASEY, A. E., FISHBEIN, W. I., ABRAMS, I. and BUNDESEN, H. N. Relative frequency of "sub-clinical" poliomyelitis: daily temperature studies on intimate contacts of infectious patients. *Am. J. Dis. Child.*, 72: 635-790, 1946.
34. NELSON, N. B. and AYCOCK, W. L. A study of the reporting of paralytic poliomyelitis in Massachusetts, 1928-1941. *Am. J. Hyg.*, 40: 163-169, 1944.
35. HOWE, H. A. and BODIAN, D. Untreated human stools as a source of poliomyelitis virus. *J. Infect. Dis.*, 66: 198-201, 1940.
36. HORSTMANN, D. M., MELNICK, J. L. and WENNER, H. A. The isolation of poliomyelitis virus from human extra-neural sources. I. Comparison of virus content of pharyngeal swabs, oropharyngeal washings, and stools of patients. *J. Clin. Investigation*, 25: 270-274, 1946.
37. LEPINE, P., SÉDALLIAN, P. and SAUTTER, V. Sur la présence du virus poliomyélique dans les matières fécales et sa longue durée d'élimination chez un porteur sain. *Bull. Acad. de méd., Paris*, 122: 141-149, 1939.
38. HOWITT, B., BUSS, W. C. and SHAFFRATH, M. D. Acute anterior poliomyelitis in Kern County, California. *Am. J. Dis. Child.*, 64: 631-648, 1942.
39. WARD, R. and WALTERS, B. The elimination of poliomyelitis virus from the human mouth or nose. *Bull. Johns Hopkins Hosp.*, 80: 98-106, 1947.
40. BELL, E. J. The relationship between the anti-poliomyelitic properties of human nasopharyngeal secretions and blood serums. *Am. J. Hyg.*, 47: 351-369, 1948.
41. GEAR, J. and MENDEL, B. The study of an outbreak of poliomyelitis occurring in a suburb of Johannesburg. *South African M. J.*, 20: 106-110, 1946.
42. BROWN, G. C., FRANCIS, T., JR. and PEARSON, H. E. Rapid development of carrier state and detection of poliomyelitis in stool nineteen days before onset of paralytic disease. *J. A. M. A.*, 129: 121-123, 1945.
43. TAYLOR, E. and AMOSS, H. L. Carriage of the virus of poliomyelitis with subsequent development of the infection. *J. Exper. Med.*, 26: 745-754, 1917.
44. GORDON, F. B., SCHABEL, F. M., CASEY, A. E. and FISHBEIN, W. I. Recovery of poliomyelitis virus from the throat during the incubation period. *J. A. M. A.*, 135: 884-888, 1947.
45. LANGMUIR, A. D. Carriers and abortive cases in a rural poliomyelitis outbreak. *Am. J. Pub. Health*, 32: 275-281, 1942.
46. PEARSON, H. E., BROWN, G. C., RENDTORFF, R. C., RIDENOUR, G. M. and FRANCIS, T., JR. Studies of the distribution of poliomyelitis virus. III. In an urban area during an epidemic. *Am. J. Hyg.*, 41: 188-210, 1945.
47. ZINTEK, A. R. The rapid infection of a family after introduction of poliomyelitis virus. *Am. J. Hyg.*, 46: 248-253, 1947.
48. HOWE, H. A. and BODIAN, D. Isolation of poliomyelitis virus from the throats of symptomless children. *Am. J. Hyg.*, 45: 219-222, 1947.
49. GORDON, F. B., SCHABEL, F. M., JR., CASEY, A. E. and FISHBEIN, W. I. Laboratory study of the epidemiology of poliomyelitis. *J. Infect. Dis.*, 82: 294-301, 1948.
50. BROWN, G. C., AINSLIE, J. D. and FRANCIS, T., JR. The incidence of poliomyelitis virus in cases of mild illness during a severe urban epidemic. *Am. J. Hyg.*, 49: 194-199, 1949.
51. SABIN, A. B. The olfactory bulbs in human poliomyelitis. *Am. J. Dis. Child.*, 60: 1313-1318, 1940.

52. HOWE, H. A. and BODIAN, D. Neuropathological evidence on the portal of entry problem in human poliomyelitis. *Bull. Johns Hopkins Hosp.*, 69: 183-215, 1941.
53. SABIN, A. B. and WARD, R. The natural history of human poliomyelitis. i. Distribution of virus in nervous and non-nervous tissues. *J. Exper. Med.*, 73: 771-793, 1941.
54. WARD, R., HORSTMANN, D. M. and MELNICK, J. L. The isolation of poliomyelitis virus from the human extra-neural sources. iv. Search for virus in the blood of patients. *J. Clin. Investigation*, 25: 284-286, 1946.
55. RIVERS, T. M. *Viral and Rickettsial Infections of Man*. Pp. 32-35. Philadelphia, 1948. J. B. Lippincott Company.
56. EKLUND, C. M. Human encephalitis of the Western equine type in Minnesota in 1941: clinical and epidemiological study of serologically positive cases. *Am. J. Hyg.*, 43: 171-193, 1946.
57. CARLSON, H. J., RIDENOUR, G. M. and MCKHANN, C. F. Effect of the activated sludge process of sewage treatment on poliomyelitis virus. *Am. J. Pub. Health*, 33: 1083-1087, 1943.
58. LENSEN, S. G., RHIAN, M. and STEBBINS, M. R. Inactivation of partially purified poliomyelitis virus in water by chlorination. ii. *Am. J. Pub. Health*, 37: 869-874, 1947.
59. RIDENOUR, G. M. and INGOLS, R. S. Inactivation of poliomyelitis virus by "free" chlorine. *Am. J. Pub. Health*, 36: 639-644, 1946.
60. LAVINDER, C. H., FREEMAN, A. W. and FROST, W. H. Epidemiologic studies of poliomyelitis in New York City and the Northeastern United States during the year 1916. *Pub. Health Bull.*, 91: 1918.
61. DINGMAN, J. C. Report of a possibly milk-borne epidemic of infantile paralysis. *New York State J. Med.*, 16: 589-590, 1916.
62. KNAPP, A. C., GODFREY, E. S. and AYCOCK, W. T. An outbreak of poliomyelitis apparently milk-borne. *J. A. M. A.*, 87: 635-639, 1926.
63. AYCOCK, W. L. A milk-borne epidemic of poliomyelitis. *Am. J. Hyg.*, 7: 791-803, 1927.
64. AYCOCK, W. L. and EATON, P. A comparison between multiple cases of measles, scarlet fever and infantile paralysis. *Am. J. Hyg.*, 5: 733-741, 1925.
65. WARD, R., MELNICK, J. L. and HORSTMANN, D. M. Poliomyelitis virus in fly-contaminated food collected at an epidemic. *Science*, 101: 491-493, 1945.
66. MELNICK, J. L., WARD, R., LINDSAY, D. R. and LYMAN, F. E. Fly-abatement studies in urban poliomyelitis epidemics during 1945. *Pub. Health Rep.*, 62: 910-922, 1947.
67. SEDDON, H. J., AGIUS, T., BERNSTEIN, H. G. G. and TUNBRIDGE, R. E. The poliomyelitis epidemic in Malta 1942-1943. *Quart. J. Med.*, 14: 1-26, 1945.
68. LEAKE, J. P., BOLTEN, J. and SMITH, H. F. Winter outbreak of poliomyelitis. *U. S. Pub. Health Rep.*, 32: 1995-2015, 1917.
69. TRASK, J. D. and PAUL, J. R. The detection of poliomyelitis virus in flies collected during epidemics of poliomyelitis. ii. Clinical circumstances under which flies were collected. *J. Exper. Med.*, 77: 545-556, 1943.
70. SABIN, A. B. and WARD, R. Flies as carriers of poliomyelitis virus in urban epidemics. *Science*, 94: 590-591, 1941.
71. MELNICK, J. L. Isolation of poliomyelitis virus from single species of flies collected during an urban epidemic. *Am. J. Hyg.*, in press.
72. NEUSTAEDTER, M. and THRO, W. C. Experimental poliomyelitis produced in monkeys from the dust of the sickroom. *New York M. J.*, 94: 813-820, 1911.
73. AYCOCK, W. L. and KESSEL, J. F. The infectious period of poliomyelitis and virus detection. *Am. J. M. Sc.*, 205: 454-465, 1943.
74. AYCOCK, W. L. Significance of age distribution of poliomyelitis; evidence of transmission through contact. *Am. J. Hyg.*, 8: 35-54, 1928.
75. SABIN, A. B. The epidemiology of poliomyelitis. Problems at home and among the armed forces abroad. *J. A. M. A.*, 134: 749-756, 1947.
76. ALLWOOD-PAREDES, J. An epidemic of acute anterior poliomyelitis in El Salvador, C. A. *Am. J. Pub. Health*, 34: 941-947, 1944.
77. SHEPLAN, L. B. and TRELLES, B. H. Infantile paralysis in Puerto Rico. *Puerto Rico J. Pub. Health & Trop. Med.*, 19: 120-131, 1943.
78. IRAZABAL, P. and IRIBARREN, R. R. Consideraciones sobre el brote de poliomieltis anterior aguda ocurrido en Caracas durante los anos de 1940-1941. *Arch. venezol. puericult. y pediat.*, 5: 1-27, 1943.
79. ANDRADE-MARIN, C. Primer brote epidemico de poliomyelitis en-Quito. *Rev. chilena de pediat.*, 16: 177-185, 1945.
80. LEVY, A. J. Poliomyelitis in Palestine. *Hebrew M. J.*, 2: 258-266, 1937.
81. PAUL, J. R., HAVENS, W. P. and VAN ROOYEN, C. E. Poliomyelitis in British and American troops in the Middle East. The isolation of virus from human feces. *Brit. M. J.*, 1: 841-843, 1944.
82. FINDLAY, G. M., ANDERSON, J. R. and HAGGIE, M. H. K. Poliomyelitis in West Africa. *J. Roy. Army M. Corps*, 86: 20-25, 1946.
83. CAUCHEY, E. and PORTEOUS, W. M. An epidemic of poliomyelitis occurring among troops in the Middle East. *M. J. Australia*, 33: 5-10, 1946.
84. GILLIAM, A. G. Changes in age selection of fatal poliomyelitis. *Pub. Health Rep.*, 63: 677-684, 1948.
85. DAUER, C. C. Trends in age distribution of poliomyelitis in the United States. *Am. J. Hyg.*, 48: 133-146, 1948.
86. BERTENIUS, B. S. On the problem of poliomyelitis. An epidemiological-statistical study. *Acta path. et microbiol. Scandinav.*, 68: 1947.
87. HORSTMANN, P. Age distribution of poliomyelitis during recent epidemics in Copenhagen. *Acta med. Scandinav.*, 124: 482-493, 1946.
88. YANKAUER, ALFRED, JR. and GOLDBERG, H. P. Age distribution of poliomyelitis in New York City in relation to previous epidemics. *Am. J. Pub. Health*, 38: 1683-1687, 1948.
89. Unpublished data from the Baltimore City Health Department.
90. BURNET, F. M. The epidemiology of poliomyelitis with special reference to the victorian epidemic of 1937-38. *M. J. Australia*, 27: 1-12, 1940.

91. BURNET, F. M. and MACNAMARA, J. Immunological differences between strains of poliomyelitis virus. *Brit. J. Exper. Path.*, 12: 57-61, 1931.
92. TRASK, J. D., PAUL, J. R., BEEBE, A. R. and GERMAN, W. J. Viruses of poliomyelitis. An immunological comparison of six strains. *J. Exper. Med.*, 65: 687-704, 1937.
93. BODIAN, D., MORGAN, I. M. and HOWE, H. A. Differentiation of types of poliomyelitis viruses. III. The grouping of 14 strains into three basic immunological types. *Am. J. Hyg.*, 49: 234-245, 1949.
94. SABIN, A. B. Epidemiological patterns of poliomyelitis in different parts of the world. *Proc. First Internat. Poliomyelitis Conference*, 1948.
95. KESSEL, J. F., MOORE, F. J. and PAIT, C. F. Differences among strains of poliomyelitis virus in *Macaca mulatta*. *Am. J. Hyg.*, 43: 82-89, 1946.
96. FISCHER, A. E. and STILLERMAN, M. Does an attack of acute anterior poliomyelitis confer adequate immunity? *J. A. M. A.*, 110: 569-572, 1938.
97. NELSON, N. B. and GREEN, W. T. Second attacks of anterior poliomyelitis: report of four cases. *Am. J. Dis. Child.*, 65: 757-762, 1943.
98. BRIDGE, E. M., CLARKE, G. H. and ABBE, D. Clinical immunity in poliomyelitis. *Am. J. Dis. Child.*, 72: 501-509, 1946.
99. ADDAIR, J. and SNYDER, L. H. Evidence for an autosomal recessive gene for susceptibility to paralytic poliomyelitis. *J. Hered.*, 33: 307, 1942.
100. AYCOCK, W. L. Familial aggregation of poliomyelitis. *Am. J. M. Sc.*, 203: 452-465, 1942.
101. WERNSTEDT, W. Clinical and epidemiological study of the second great epidemic of poliomyelitis in Sweden, 1911-1913. *Ergebn. d. inn. Med. u. Kinderh.*, 26: 248-350, 1924.
102. BRODIE, M. Active immunization in monkeys with inactivated virus. *J. Immunol.*, 28: 1-18, 1935.
103. MORGAN, I. M. Immunization of monkeys with formalin-inactivated poliomyelitis viruses. *Am. J. Hyg.*, 48: 394-406, 1948.
104. MILZER, A., OPPENHEIMER, F. and LEVINSON, S. O., A new method for the production of potent inactivated vaccines with ultraviolet irradiation. III. A completely inactivated poliomyelitis vaccine with the Lansing strain in mice. *J. Immunol.*, 50: 331-340, 1945.
105. HOWE, H. A. and BODIAN, D. *Neural Mechanisms in Poliomyelitis*. New York, 1942. The Commonwealth Fund.

Viruses of Poliomyelitis^{*}

ROBERT WARD, M.D.

New York, New York

THE etiologic agent of human poliomyelitis is a virus which can be identified by the characteristic experimental disease it produces in primates, by its limited host range, by the character and distribution of microscopic lesions in the central nervous system (CNS) of the infected host, by its immunologic characteristics and by certain physical and chemical properties.

EXPERIMENTAL DISEASE

The first step in recognition of the poliomyelitis virus is to inoculate suitably prepared material into primates. Virus is most commonly detected during life in human intestinal excreta and material from the oropharynx and at postmortem from the central nervous system and contents of the lower bowel. The routes commonly used are the intracerebral, intranasal, intraperitoneal, intra- and subcutaneous and oral. The most sensitive test is usually afforded by direct contact of virus with nervous tissue. The rhesus monkey (*Macaca mulatta*) is the species most often employed. The chimpanzee (*Pan satyrus*) and the cynomolgous monkey (*Macaca irus*) are especially susceptible to oral administration of virus. After a variable incubation period (average of one to two weeks) the monkey may develop the typical experimental disease characterized by a fever of 105° F. or more, excitement, ruffled fur, tremors of the head and extremities followed by partial or complete paralysis of one or more extremities. Although separate involvement of most of the cranial nerves has been described, the one most commonly recognized is the seventh. The monkey may be quickly rendered prostrate and death may

follow even if careful nursing care is supplied. Other phenomena exhibited by experimental animals may also resemble the disease in man. Paralysis or localized weakness may be transitory, lasting a day or so. The animal may have fever and other premonitory signs but no detectable weakness, or it may exhibit no "clinical" disturbance whatever and still present the typical microscopic lesions of poliomyelitis in the CNS from which virus can be recovered on passage.

Pathologic Changes. The typical microscopic lesions consist of necrosis of the nerve cells, neuronophagia and perivascular cellular infiltration. The character and distribution of these lesions so important in the identification of poliomyelitis virus are described in detail in Bodian's article in this series.¹

Physical and Chemical Properties. On the basis of filtration experiments the size of poliomyelitis virus is estimated to be about 8 to 17 millimicra in diameter.^{2,3} More recently Gard has reported from data obtained from the electron microscope and sedimentation and diffusion constants that the FA encephalomyelitis virus of mice is a thread-like particle 12.5 by 580 millimicra, and he has also observed similar thread-like particles in preparations made from human stools.⁴ Melnick described similar rod-shaped particles in purified stools containing poliomyelitis virus.⁵ The significance of these rod-shaped particles was thrown in doubt when similar particles were observed in normal children's stools which were negative for active virus. Loring et al.,⁶ on the other hand, studied purified preparations of Lansing virus by electromicrography and observed slightly asymmetric particles,

^{*} From the Department of Pediatrics, New York University College of Medicine, New York, N. Y.

with an average diameter of 25 millimicra. As similar particles have been obtained from the CNS of normal animals it is not possible to state with assurance that poliomyelitis virus has yet been seen or measured.

The action of certain physical and

Host Range. A definition of the term poliomyelitis virus is not easily made and its subgroups are not easily classified.¹² But the pathogenicity for various laboratory animals is an important step leading to its identification for, in contrast to other

TABLE I
HOST RANGE OF POLIOMYELITIS VIRUS COMPARED WITH CERTAIN OTHER NEUROTROPIC VIRUSES

Virus	Monkey	Mouse	Cotton Rat	Hamster	Guinea Pig	Rabbit	Hen's Egg
Poliomyelitis	+	0	0	0	0	0	0
Poliomyelitis (Lansing group) . . .	+	+	+	+	0	0	0
Theiler's (mouse encephalomyelitis)	0	+	+	+	0	0	+
MM, Columbia SK, EMC	?	+	+	+	+	0	+
Encephalitis (St. Louis type)	+	+	?	+	0	0	+
Lymphocytic choriomeningitis . . .	+	+	+	+	+	0	+
Encephalitis (equine types)	+	+	+	+	+	+	+
Rabies	+	+	+	+	+	+	+
Herpes simplex	0	+	+	+	+	+	+

chemical agents on poliomyelitis virus indicates that in some respects it is a hardy virus. It has been preserved for years in the frozen state (−20°c. or −70°c.)⁷ or in 50 per cent buffered glycerol at ordinary icebox temperature. Ether appears to have little if any harmful effect on the virus. This fact is especially useful in the laboratory for preparing contaminated material such as stools, sewage, etc. for inoculation into monkeys. The virus is not affected in the pH range of 4 to 10⁸ nor by 1 per cent phenol. On the other hand, it is destroyed by such protein-denaturing agents as heat, ultraviolet light, chlorine, hydrogen peroxide, potassium permanganate and formalin. Recent studies have shown that it is easier to heat-inactivate certain strains of virus pathogenic for rodents when this virus is suspended in water rather than in milk.⁹ By the same token the presence of organic matter appears to protect virus against chlorine.¹⁰ It is probable that more chlorine is needed to destroy poliomyelitis virus than most bacteria¹⁰ although this point has not been settled.¹¹

neurotropic viruses, most strains of poliomyelitis virus are pathogenic only for man and other primates, thus serving to distinguish poliomyelitis from various types of encephalitis virus, some of which are pathogenic for mice, others for guinea pigs and rabbits also. (Table 1.) The Lansing strain of poliomyelitis virus was first isolated and adapted by Armstrong from monkeys to cotton rats and mice.¹²⁻¹⁴ Since then a few others related immunologically to the Lansing strain have been similarly adapted to rodents.^{15,16} Reports of the adaptation of Lansing-like strains direct from man to rodents^{17,18} have not been confirmed. It is striking that poliomyelitis virus has not been shown to propagate in the embryonated hen's egg; very few viruses which attack man fail in this respect. In the process of "adapting" viruses to various experimental animals one has to be on guard against the accidental recovery of agents native to the experimental host. Theiler's virus of mouse encephalomyelitis is a case in point. The TO strains of this mouse virus bear a close resemblance to poliomyelitis virus, both

having the same size, similar reactions to certain physical and chemical agents, similar distribution in the bodies of their respective natural hosts and they are productive of similar pathologic lesions. Furthermore, only 1 of 1,000 to 10,000 mice develops spontaneous paralysis, an incidence which appears to have a remarkable parallel in human poliomyelitis. The difference in host spectrums between poliomyelitis and Theiler's virus is shown in Table 1. Immunologic methods may also serve to differentiate these agents.

The so-called MM virus and Columbia SK virus, considered by some as strains of poliomyelitis, have recently been shown to be immunologically indistinguishable from encephalomyocarditis (EMC) virus.^{19,20} The host range of this group of viruses is not that of poliomyelitis and, furthermore, MM virus is killed by ether.²⁹ These differences indicate that by present criteria MM and Columbia SK viruses do not conform to the pattern of orthodox poliomyelitis viruses. The possibility of their relation to disease in man needs further study.

Immunologic Characteristics. The problem of multiple strains of poliomyelitis virus distinguishable by immunologic methods is fully dealt with in the article by Morgan.²¹

POLIOMYELITIS IN MAN

Distribution of the Poliomyelitis Virus. Studies of the pattern of distribution of virus postmortem in man have increased our knowledge of the natural history of the disease and, taken together with the finding of abundant virus in stools, sewage, flies and fly-contaminated food, they have served to re-orient the epidemiologist concerned with portals of entry and pathways of transmission. Instead of being found generally in all tissues and organs of the body, virus is localized chiefly in the alimentary tract and central nervous system.²²⁻²⁴ In the alimentary tract virus is detectable at various levels from mouth to anus, in the washed walls as well as in the contents. Thus it was found in the tongue, pharyngeal wall with or without tonsils, the washed walls and, in

separate tests, in the contents of both small and large intestines. In the CNS virus was found not generally disseminated, as in rabies and equine encephalomyelitis, but localized in certain specific areas in close agreement with the distribution of pathologic lesions and with its progress along closed neuronal pathways. Virus was detected at all levels of the spinal cord, pons and medulla, mesencephalon, diencephalon and motor cortex. None was found in the frontal and occipital cortexes, in the olfactory bulbs or anterior perforated substance. The last two, taken in conjunction with the usual absence of virus from the nasal mucosa and nasal secretions,^{25,26} points away from the nose as a common portal of entry. Furthermore, the absence of virus from other peripheral collections of cells of the autonomic nervous system (salivary glands, superior cervical sympathetic ganglia, adrenal glands and urinary bladder wall) indicates no centrifugal spread to those areas. Its presence, therefore, in the wall of the alimentary tract strongly suggests that tissue as a primary site of attack and invasion.

Virus has been found but rarely in the blood^{17,27} which, correlated with the previously mentioned data, indicates that the blood stream is neither an important nor necessary factor in the pathogenesis of poliomyelitis. The significance of the occasional postmortem detection of virus in certain viscera and lymph nodes is unknown.²²⁻²⁴

Elimination of the Virus. Poliomyelitis virus has been recovered frequently from washings of the oropharynx and nasopharynx, from pharyngeal swabs and from intestinal excreta. In a limited number of tests no virus was found in the urine.²⁵ In their summary of the literature up to 1938, Vignec, Paul and Trask²⁸ found that virus had been detected in material from the nasopharynx, tonsils and trachea in 15 per cent of 105 attempts made during the first five days of illness and in 7 per cent of 182 attempts made thereafter. Sabin and Ward²⁵ on the other hand found no virus in nasal secretions collected on cotton plugs or in

saliva from twenty patients in the first two weeks of illness. Kessel and his associates were unable to detect virus in the nasal washings of 139 patients.²³ Later Howe and his group^{30,31} demonstrated virus in almost one-half of the pharyngeal swabs taken during the first three days of illness. Results were negative on swabs taken later in the disease. These findings have been generally confirmed in other laboratories.^{26,32-34}

During the last decade the emphasis has been on intestinal excreta as the mode of exit in man. Numerous investigators frequently have detected virus in the stools of patients with paralytic as well as non-paralytic poliomyelitis and in those of healthy carriers as well. Virus seems to be present in higher incidence and to persist for longer periods in the stool than in material from the oropharynx. Thus Horstmann, Melnick and Wenner³⁵ recovered virus during the first week of illness from the stools of seven of ten patients but from the oropharynx of only two of nineteen patients tested; of specimens collected during the second week, four of seven stools, but not one of seven specimens from the oropharynx, yielded virus. Horstmann, Ward and Melnick³⁶ have shown that the excretion of virus in stools persists appreciably for eight weeks. The record is held by Lépine, Sédallian and Sautter³⁷ who detected virus in the stool of a patient as long as 123 days after onset. Of perhaps even greater interest and importance is the detection of virus in the stool *nineteen days before* onset of paralytic poliomyelitis by Brown, Francis and Pearson.³⁸ Similar findings have been reported in the pharynx by Gordon and his group.³⁴ These studies provoke a number of important questions: In what tissue is virus being elaborated that it may be excreted for so long before and after the appearance of clinical signs? To what degree is the population "infested" before an outbreak? What are the factors, controllable or not, related to the host, virus or environment which determine the conversion of inapparent or non-paralytic poliomyelitis to the paralytic form of the disease?

REFERENCES

1. BODIAN, DAVID. Histopathologic basis of clinical findings in poliomyelitis. *Am. J. Med.*, 6: 563, 1949.
2. THEILER, M. and BAUER, J. H. Ultrafiltration of the virus of poliomyelitis. *J. Exper. Med.*, 60: 767, 1934.
3. ELFORD, W. J., GALLOWAY, I. A. and PERDRAU, J. R. The size of the virus of poliomyelitis as determined by ultrafiltration analysis. *J. Path. & Bact.*, 40: 135, 1935.
4. GARD, S. Purification of poliomyelitis viruses; experiments on murine and human strains. 173 pp., Uppsala, Almqvist & Wiksells, 1943; *Acta med. Scandinav.*, 143: 1-173, 1943.
5. MELNICK, J. L. Detection with electron microscope of rod-shaped particles in stools of normal and poliomyelitic individuals. *J. Immunol.*, 48: 1, 1944.
6. LORING, H. S., MARTON, L. and SCHWERDT, C. E. Electron microscopy of purified Lansing virus. *Proc. Soc. Exper. Biol. & Med.*, 62: 291, 1946.
7. MELNICK, J. L. Storage of mouse-adapted strains of poliomyelitis virus and of Japanese B encephalitis virus at subfreezing temperatures. *J. Infect. Dis.* 79: 27, 1946.
8. LORING, H. S. and SCHWERDT, C. E. Studies on purification of poliomyelitis virus; pH stability range of MVA strain. *Proc. Soc. Exper. Biol. & Med.*, 57: 173, 1944.
9. LAWSON, R. B. and MELNICK, J. L. Inactivation of murine poliomyelitis viruses by heat. *J. Infect. Dis.*, 80: 201, 1947.
10. TRASK, J. D., MELNICK, J. L. and WENNER, H. A. Chlorination of human, monkey-adapted and mouse strains of poliomyelitis virus. *Am. J. Hyg.*, 41: 30, 1945.
11. LENSEN, S. G., RHIAN, M. and STEBBINS, M. Inactivation of partially purified poliomyelitis virus in water by chlorination, II. *Am. J. Pub. Health*, 37: 869, 1947.
12. ARMSTRONG, C. The experimental transmission of poliomyelitis to the eastern cotton rat, *Sigmodon hispidus hispidus*. *Pub. Health Rep.*, 54: 1719, 1939.
13. ARMSTRONG, C. Successful transfer of the Lansing strain of poliomyelitis virus from the cotton rat to the white mouse. *Pub. Health Rep.*, 54, 2302, 1939.
14. ARMSTRONG, C. Studies on choriomeningitis and poliomyelitis. *Tr. & Stud., Coll. Physicians, Philadelphia*, 8: 1, 1940.
15. SCHLESINGER, R. W., MORGAN, I. M. and OLITSKY, P. K. Transmission to rodents of Lansing type poliomyelitis virus originating in the middle east. *Science*, 98: 452, 1943.
16. MELNICK, J. L., and WARD, R. Unpublished data.
17. KAPROWSKI, H., NORTON, T. W. and McDERMOTT, W. Isolation of poliomyelitis virus from human serum by direct inoculation into a laboratory mouse. *Pub. Health Rep.*, 62: 1467, 1947.
18. MILZER, A. and BYRD, CHESTER, L. Autolyzed brain tissue as a means of facilitating transmission of experimental poliomyelitis. *Science*, 105: 70, 1947.
19. WARREN, J. and SMADEL, J. E. A serological relationship between the virus of encephalomyocarditis and certain strains of poliomyelitis-like viruses. *Federation Proc.*, 7: 311, 1948.
20. WARD, R. and RADER, D. L. Unpublished observations.

21. MORGAN, ISABEL M. Mechanism of immunity in poliomyelitis and its bearing on differentiation of types. *Am. J. Med.*, 6: 556, 1949.
22. SABIN, A. B. and WARD, R. Natural history of human poliomyelitis; distribution of virus in nervous and non nervous tissues. *J. Exper. Med.*, 73: 771, 1941.
23. KESSEL, J. F., MOORE, F. J., STIMPERT, F. D. and FISK, R. T. Occurrence of poliomyelitis virus in autopsies, patients, and contacts. *J. Exper. Med.*, 74: 601, 1941.
24. WENNER, H. A. and PAUL, J. R. Fatal infection with poliomyelitis virus in a laboratory technician. Isolation of virus from lymph nodes. *Am. J. M. Sc.*, 213: 9, 1947.
25. SABIN, A. B. and WARD, R. Natural history of human poliomyelitis; elimination of virus. *J. Exper. Med.*, 74: 519, 1941.
26. WARD, R. and WALTERS, B. The elimination of poliomyelitis virus from the human mouth or nose. *Bull. Johns Hopkins Hosp.*, 80: 98, 1947.
27. WARD, R., HORSTMANN, D. M. and MELNICK, J. L. The isolation of poliomyelitis virus from human extra-neural sources. iv. search for virus in the blood of patients. *J. Clin. Investigation*, 25: 284, 1946.
28. VIGNEC, A. J., PAUL, J. R. and TRASK, J. D. Recovery of virus of poliomyelitis from extra-neural sources in man, with survey of literature. *Nale J. Biol. & Med.*, 11: 15, 1938.
29. LO GRIPPO, G. A. and WARD, R. Unpublished observations.
30. HOWE, H. A., WENNER, H. A., BODIAN, D. and MAXCY, K. F. Poliomyelitis virus in human oropharynx. *Proc. Soc. Exper. Biol. & Med.*, 56: 171, 1944.
31. HOWE, H. A., BODIAN, D. and WENNER, H. A. Further observations on the presence of poliomyelitis virus in the human oro-pharynx. *Bull. Johns Hopkins Hosp.* 76: 19, 1945.
32. WENNER, H. A. and TANNER, W. A. Widespread distribution of poliomyelitis in households attacked by the disease. *Proc. Soc. Exper. Biol. & Med.*, 66: 92, 1947.
33. PEARSON, H. E. and BROWN, G. C. Recovery of virus from throats of poliomyelitis patients. *Proc. Soc. Exper. Biol. & Med.*, 66: 503, 1947.
- 34a. GORDON, F. B., SCHABEL, F. M., JR., CASEY, A. E. and FISHBEIN, W. I. Recovery of poliomyelitis virus from the throat during the incubation period. *J. A. M. A.*, 135: 884, 1947.
- 34b. SCHABEL, F. M., CASEY, A. E., FISHBEIN, W. I., SMITH, H. T. and BUNDESEN, H. N. Isolation of poliomyelitis virus from human stools during the incubation period. *Proc. Soc. Exper. Biol. & Med.*, 68, 593, 1948.
35. HORSTMANN, D. M., MELNICK, J. L. and WENNER, H. A. The isolation of poliomyelitis virus from human extra-neural sources. i. Comparison of virus content of pharyngeal swabs, oropharyngeal washings and stools of patients. *J. Clin. Investigation*, 25: 270, 1946.
36. HORSTMANN, D. M., WARD, R. and MELNICK, J. L. The isolation of poliomyelitis virus from human extra-neural sources. iii. persistence of virus in stools after acute infection. *J. Clin. Investigation*, 25: 278, 1946.
37. LÉPINE, P., SÉDALLIAN, P. and SAUTTER, V. Sur la présence du virus poliomyélique dans les matières fécales et sa longue durée d'élimination chez un porteur sain. *Bull. Acad. de méd., Paris*, 122: 141, 1939.
38. BROWN, G. C., FRANCIS, T. and PEARSON, H. Rapid development of carrier state and detection of poliomyelitis virus. *J. A. M. A.*, 129: 121, 1945.

Mechanism of Immunity in Poliomyelitis and Its Bearing on Differentiation of Types*

ISABEL M. MORGAN, PH.D.

Baltimore, Maryland

IN this paper I will present the concept of immunity to poliomyelitis as it has been developed in the last few years. This concept has been based largely on experimental work using monkeys and chimpanzees and, for certain purposes, cotton rats and mice. Direct observations on human beings, naturally more limited in scope, will also be discussed.

Since discovery of the virus etiology of poliomyelitis, more attention has been given to the pathogenesis of the virus than to its immunogenesis, that is, the immune response which develops in the wake of infection. With the evidence available, I will give the basis for the current understanding of immunity in man, whether acquired without obvious illness or as a result of known infection. To understand the epidemiology or immunology of a disease entity it is obviously essential to know whether the causative agent is a single or multiple immunologic type. Thus an important addition to the understanding of poliomyelitis is the information we are gaining on the immunologic types of the virus.

IMMUNIZATION

Of Monkeys with Active Virus. Earlier attempts to immunize monkeys with active virus have already been reviewed.¹ Among them the outstanding ones are those of Kramer, Grossman and Hoskwith² and Aycock and Kagan.³ They produced circulating antibody and intracerebral immunity in monkeys vaccinated with active virus.

In this laboratory we have also vaccinated monkeys with active virus. We have found

the intramuscular route superior to other peripheral routes for inducing active immunity.¹ Monkeys vaccinated by repeated injections of active virus by this route have resisted intracerebral challenge with a large dose of the same strain of virus as used for immunization. The monkeys also developed neutralizing antibody demonstrable at a high level in the serum. Use of the Lansing strain of virus infective in rodents⁴ has facilitated these studies. With this virus, it is possible to carry out quantitative neutralization tests in mice. It was found that the higher the level of circulating antibody, the greater was the proportion of animals immune to intracerebral challenge.⁵ Based on these quantitative results the serum antibody level necessary to insure immunity was established. Although immune animals have a high level of antibody in the serum, that in the CNS and spinal fluid is far lower. The picture of antibody distribution in the actively immunized animal will be contrasted later with that in the paralyzed convalescent.

The effect of vaccination is not transient for antibody has been demonstrated in the serum of three immune monkeys for as long as one year after the last vaccination.

Of Monkeys with Inactivated Virus. Several investigators have attempted to vaccinate monkeys with poliomyelitis virus inactivated by a variety of agents. Some reported production of antibody but not intracerebral immunity. The more careful studies of Brodie^{6,7} with virus inactivated with formalin indicated the possibility of intracerebral immunity to minimal doses of

* From The Poliomyelitis Research Center, Department of Epidemiology, Johns Hopkins University, Baltimore, Md. Aided by a grant from The National Foundation for Infantile Paralysis, Inc.

virus. The results have been critically reviewed.⁸ It may be stated simply here that although his criterion for inactivation was far better than that of earlier workers, the minimal doses used for challenge make the claim of intracerebral immunity questionable.

We have also vaccinated monkeys with virus inactivated with formalin.⁸ After repeated intramuscular injections the majority became immune to a large intracerebral dose of active virus. The serum antibody level in these monkeys equalled that in monkeys vaccinated with active virus. Thus the immunogenic effect of active virus has been reproduced in monkeys by virus inactivated by formalin, more extensive immunization with the inactivated virus being required. Although this result gives promise that a safe vaccine might be developed, many obstacles will have to be overcome before considering vaccination in man. A readily available source of virus is needed. In order to develop a more efficient vaccine much animal experimentation remains to be done. Complete inactivation must be established by the most stringent tests available since with a disease of such low incidence one would not be justified in taking any risk whatsoever in the vaccination procedure. Finally, a human trial would have to be carried out for efficacy of vaccination. Because of the low incidence of the paralytic disease, this would require a vast human experiment. Gilliam and Onstott⁹ have estimated, based on an expected epidemic rate, that an adequate field trial would require at least 15,000 children.

In Paralytic Convalescent Monkeys. Several investigators have studied second attacks of poliomyelitis by re-injection of monkeys convalescent from one attack. The results have been conflicting. For the present it will simplify the question to deal with results in which the same strain of virus was used for first and second inoculations. Kessel and Pait¹⁰ reported sixty-three of sixty-five individuals refractory to second attacks after re-inoculation with the strain inducing

the first attack. Bodian¹¹ observed no fresh paralysis in seventy-seven monkeys re-inoculated intracerebrally with the same or immunologically related strains. Howe and Bodian¹² found that monkeys uniformly failed to develop fresh paralysis when re-inoculated in an area of the CNS which had been infected earlier with the same virus. However, monkeys in which only part of the CNS had been infected were fully susceptible to virus introduced by a previously uninvaded portal. For example, they isolated the lower part of the CNS by spinal cord transection. The CNS of monkeys so prepared was then infected with virus injected into the CNS below the level of transection. When subsequently the CNS above was exposed to virus, it was found to be fully susceptible.

An interesting interpretation of these findings lies in the distribution of antibody in the paralytic convalescent animal. It was found¹³ that the highest antibody levels were within the central nervous system. The areas most heavily involved with poliomyelitis, namely, the anterior horn of the spinal cord, and next the medulla, showed the greatest concentration of antibody. Non-susceptible gray matter and white matter showed little or no antibody. The level in serum, equal to that in spinal fluid, was well below that in the affected gray matter. The finding of a high concentration of antibody in the areas of the CNS most heavily involved not only accounts for the immunity to second attack but also explains why, in the experiments of Howe and Bodian, no such immunity was found in those parts of the CNS which had been isolated from the first infection.

TYPE DIFFERENTIATION OF STRAINS OF POLIOMYELITIS VIRUS BY RECIPROCAL VACCINATION-IMMUNITY

For the first two decades after discovery of the virus etiology of poliomyelitis, strains of the virus were used for experimental work in monkeys with little consideration of the relationship of one to another. The demonstration that active immunity of a high

order could be induced in monkeys in response to intramuscular injection of active poliomyelitis virus¹ has afforded a basis for type differentiation.¹⁴ The relationship of one strain to the other can be determined by reciprocal vaccination and intracerebral

have now been typed by the method of cross-immunity.¹⁵ All but one of these have been shown to be more closely related to one than to the other of two types of which the Lansing and Brunhilde strains are prototypes. Nine fell into the Brunhilde and

TABLE I
RELATIONSHIP OF FOUR STRAINS OF POLIOMYELITIS BY RECIPROCAL VACCINATION-IMMUNITY

Vaccinated with, and Immune to:	Intracerebral Challenge with:			
	Lansing	Brunhilde	Kotter	Frederick
Lansing.....	8/8* (i.n.)	6/8 (i.n.)†	5/5
Brunhilde.....	4/4	0/4	0/5
Kotter.....	6/8	0/4	0/4
Frederick.....	4/5	0/5	0/5	
Controls.....	34/34	19/19	21/22	19/21

* Eight monkeys paralyzed of eight challenged.
† i.n. = intranasal challenge.

challenge. This method will be illustrated by the results obtained with four strains of virus. Monkeys were vaccinated by repeated subcutaneous and intramuscular injections of active virus of one of the strains indicated in Table I. They were then challenged with an intracerebral injection of a dose of the same virus containing 10,000 infectious units. Those which proved immune were given an intramuscular step-up dose of homologous virus and then challenged with the large intracerebral dose of an unknown virus. The large intracerebral challenge dose insures a control rate of 90 per cent or over as shown in the accumulated results at the bottom of the table.

It may be seen that the response of these immune animals to the test virus is virtually all or none. The monkeys in groups vaccinated with and immune to either Brunhilde, Kotter or Frederick were also solidly immune to the other two strains. They were not immune to Lansing virus, nor were Lansing-immune animals resistant to these three viruses. The three viruses, Brunhilde, Kotter and Frederick, therefore constitute one type and Lansing another.

Fourteen strains of poliomyelitis virus

four into the Lansing type. The Leon virus proved to be not related to these two types and thus represents a third distinct type. Although to date three immunologic types of poliomyelitis virus have been found, the possibility remains that more types will be forthcoming as additional strains are classified.

TYPE DIFFERENTIATION OF STRAINS OF
POLIOMYELITIS VIRUS BY SECOND ATTACK
RATES IN CONVALESCENT MONKEYS

It has already been stated that paralytic convalescent monkeys are immune to reinoculation of the strain of virus which induced the first attack. The question of whether a different strain of poliomyelitis virus can induce a fresh attack was first clearly answered by Burnet and Macnamara¹⁶ in 1931. Monkeys convalescent from paralysis induced by a Melbourne strain succumbed to re-injection with the MV strain from New York. The converse was also true in a single MV convalescent monkey.

On the basis of resistance of convalescents (as well as of serum neutralization tests) Paul and Trask¹⁷ and Trask, Paul, Beebe

and German¹⁸ also reported qualitative immunologic differences between strains. Kessel, Stimpert and Fisk¹⁹ and later Kessel and Stimpert²⁰ found a difference in paralytic rates in convalescent monkeys when re-inoculated with the same compared with

challenge with each of the other three viruses. It is interesting that such a second attack rate in a larger experience is quite consistently around 50 per cent. The nature of this resistance of half the animals is not fully understood. The Lansing strain was

TABLE II
RELATIONSHIP BETWEEN FOUR STRAINS OF POLIOMYELITIS VIRUS BASED ON SECOND ATTACKS
IN CONVALESCENT MONKEYS

Convalescent from Attack with:	Intracerebral Challenge with:			
	Lansing	Brunhilde	Kotter	Frederick
Lansing.....	0/6*	1/2	1/3	3/3
Brunhilde.....	8/20	0/12	0/8	0/5
Kotter.....	4/11	0/7	0/8	0/6
Frederick.....	19/32	0/7	0/9	0/9
Controls....	26/28	18/18	22/24	20/22

* 0 monkeys showed fresh paralysis of six challenged.

other strains of poliomyelitis virus. These reports laid the basis for the concept that all strains of poliomyelitis virus do not behave alike in monkeys convalescent from infection with one strain. Nevertheless, it was difficult from these data to obtain a clear idea of the relationships between strains.

In our current undertaking to classify strains of poliomyelitis Bodian¹¹ has used second-attack rate in convalescent monkeys as another means of type differentiation. Table II illustrates the relationship between four strains as established by this method. The first and second intracerebral doses each containing 10,000 infectious units were injected into both sides of the thalamus.

It may be seen that animals convalescent from one strain were uniformly resistant to second attack with the same strain. Furthermore, this resistance obtained reciprocally among the three strains, Brunhilde, Kotter and Frederick. However, Lansing challenge induced paralysis in some individuals in each group of animals convalescent from Brunhilde, Kotter and Frederick infection; and, conversely, some Lansing convalescents were paralyzed by

found to be different from the other three strains which were indistinguishable from each other in these tests. Thus the relationship among these four strains obtained by vaccination-immunity is borne out by the difference in second attack rates in the convalescent.

IMMUNITY TO POLIOMYELITIS IN MAN

Naturally Acquired. Several observations bearing on immunogenesis have been made directly in man. An outstanding feature of paralytic poliomyelitis is the age incidence, the highest attack rates being in the first decade of life. Increasing evidence is accumulating that for every paralytic case there are many non-paralytic infections. Howe²¹ estimates one hundred inapparent infections for every recognized case. Another pertinent observation is that with increasing age a greater proportion of the population has a circulating neutralizing antibody. Among reports of many authors that of Turner, Young and Maxwell may be cited.²² They studied serum of 303 children and found that 86 per cent by the age of ten to fourteen years had developed neutralizing antibody to the Lansing strain. Thus it

appears that increasing antibody with the age of the population parallels a decrease in incidence in the paralytic disease. I do not mean to imply that circulating antibody, *per se*, is responsible for immunity. This is probably not the case since the blood stream is not involved in the pathogenesis of the virus. The finding of antibody in nasopharyngeal secretions²³ of individuals with a high level of circulating antibody may have a far more direct bearing on protection of the individual. This is of particular interest in view of the fact that this region, more specifically the oropharynx, is considered one of the probable portals of entry of the virus. Virus has been recovered from the oropharynx repeatedly, not only from patients with poliomyelitis²⁴ but from healthy children, playground contacts of these patients.²⁵

Naturally acquired immunity is then explained by exposure to virus which in most individuals does not produce paralytic disease but gives rise to an effective immune response. Confirmatory evidence for this hypothesis comes from the observation that chimpanzees, also susceptible to alimentary infection, develop neutralizing antibody after receiving virus by mouth in the absence of paralysis.

Since more than one immunologic type of poliomyelitis exists, full immunity in the adult must depend on prior exposure to all prevalent types of virus.

Passively Acquired. Since naturally acquired active immunity appears to be effective in protecting against poliomyelitis, the possibility of prophylactic passive immunization has frequently been raised. So far the results by chimpanzee experiment have been negative; no evidence of passive immunity to oral inoculation of virus was obtained in three chimpanzees receiving intraperitoneal injection of large quantities of homologous immune serum from vaccinated monkeys.²⁶

The use of adult human serum has been proposed for prophylaxis in children on the rationale that most adult sera have anti-poliomyelitis neutralizing power (as shown

with Lansing type virus). In fact, many children in epidemic areas have been given adult human serum in the hope that it might have a prophylactic effect. However, the possible beneficial effect of such treatment has never been adequately measured by a human experiment. Even if an effective amount of antibody could be given to children when an epidemic seemed imminent, the expected duration of two or three weeks of such passive immunization would be inadequate to protect children even through the remainder of the epidemic and such immunization would, of course, leave no permanent effect.

Adult human serum has also been proposed and used for therapy. However, the effect has been extremely difficult to evaluate. The best controlled study is that of Bahlke and Perkins²⁷ who gave human adult gamma globulin to alternate pre-paralytic patients with poliomyelitis (a total of 111) entering the hospital in Buffalo and Elmira, N. Y. in the epidemic of 1944. Their criteria for diagnosis of a preparalytic patient consisted of (1) a spinal cell count of 10 or more cells per cu. mm. and (2) no definite weakness of any muscle group, nor evidence of facial, pharyngeal or respiratory involvement in an individual who otherwise presented a clinical syndrome indicative of poliomyelitis. The patients were followed for six months by physicians who did not know which were the treated patients. No benefit from the gamma globulin was detectable.

As a Result of Paralytic Infection. Immunity in the human convalescent, by analogy with the convalescent monkey, is interpreted as based on the presence of high concentration of antibody in the affected susceptible parts of the CNS. Nevertheless, well authenticated second attacks of paralyzing poliomyelitis in man have been reported.^{11,28} According to information now available, second attacks can be attributed to fresh infection with an immunologically different type of poliomyelitis virus.

As a Result of Paralyzing Infection. There are abundant reports of the serum antibody

status of paralytic convalescent individuals. The consensus has been that they do not differ from individuals who have had no known attack of poliomyelitis. Now that we are aware of distinct immunologic types of poliomyelitis virus it is obvious that such surveys of antibody in convalescents has little meaning unless the virus used is known to be the same immunologic type as that which produced the disease. This objection has been overcome in a recent report by Hammon and Roberts²⁹ who studied serum neutralizing antibody to the strain of virus isolated directly from the patient. Each of seven patients showed serum neutralizing antibody to his own strain within six days after onset of paralysis. Of the four patients in whom titrations were done serum antibody in three had risen by forty-five days but not in one at twenty-four days after onset. These results indicate that human convalescents possess circulating antibody to infecting virus by the time of onset of paralysis; the level of antibody increases by one month in convalescence.

I have tried to bring the concept of immunity to poliomyelitis, so long relegated to a separate category, up-to-date according to findings of the last few years. Now, forty years since Landsteiner³⁰ successfully transmitted the disease to monkeys, the picture of the disease process and the ensuing immunity is becoming clearer. We hope that further understanding may some day enable us to arrest or prevent this paralytic disease.

REFERENCES

- MORGAN, I. M., HOWE, H. A. and BODIAN, D. The role of antibody in experimental poliomyelitis. ii. Production of intracerebral immunity in monkeys by vaccination. *Am. J. Hyg.*, 45: 379-389, 1947.
- KRAMER, S. D., GROSSMAN, L. H. and HOSKWITH, B. Active immunization against poliomyelitis. A comparative study. iv. Experimental immunization of monkeys with purified virus, absorbed on Al(OH)₃. *J. Immunol.*, 31: 199-208, 1936.
- AYCOCK, W. L. and KAGAN, J. R. Experimental immunization in poliomyelitis. *J. Immunol.*, 14: 85-99, 1927.
- ARMSTRONG, C. Successful transfer of the Lansing strain of poliomyelitis virus from the cotton rat to the white mouse. *Pub. Health Rep.*, 54: 2302, 1939.
- MORGAN, I. M. Level of serum antibody associated with intracerebral immunity in monkeys vaccinated with poliomyelitis virus. To be published.
- BRODIE, M. Active immunization against poliomyelitis. *Am. J. Pub. Health*, 25: 54-67, 1935.
- BRODIE, M. Active immunization in monkeys against poliomyelitis with germicidally inactivated virus. *J. Immunol.*, 28: 1-18, 1935.
- MORGAN, I. M. Immunization of monkeys with formalin-inactivated poliomyelitis viruses. *Am. J. Hyg.*, 48: 394-406, 1948.
- GILLIAM, A. G. and ONSTOTT, R. H. Results of field studies with the Brodie poliomyelitis vaccine. *Pub. Health Rep.*, 51: 160-171, 1936.
- KESSEL, J. F. and PAIT, C. F. Resistance of convalescent *Macaca mulatta* to challenge with homologous and heterologous strains of poliomyelitis virus. *Proc. Soc. Biol. & Med.*, 68: 606-608, 1948.
- BODIAN, D. Differentiation of types of poliomyelitis viruses. i. Reinfection experiments in monkeys (second attacks). *Am. J. Hyg.*, 49: 200-224, 1949.
- HOWE, H. A. and BODIAN, D. Poliomyelitis in the chimpanzee; a clinical-pathological study. *Bull. Johns Hopkins Hosp.*, 69: 149-182, 1941.
- MORGAN, I. M. The role of antibody in experimental poliomyelitis. iii. Distribution of antibody in and out of the central nervous system in paralyzed monkeys. *Am. J. Hyg.*, 45: 390-400, 1947.
- MORGAN, I. M. Differentiation of types of poliomyelitis viruses. ii. By reciprocal vaccination-immunity experiments. *Am. J. Hyg.*, 49: 225-233, 1949.
- BODIAN, D., MORGAN, I. M. and HOWE, H. A. Differentiation of types of poliomyelitis viruses. iii. The grouping of 14 strains into three basic immunological types. *Am. J. Hyg.*, 49: 234-245, 1949.
- BURNET, F. M. and MACNAMARA, J. Immunological differences between strains of poliomyelitic virus. *Brit. J. Exper. Path.*, 12: 57-61, 1931.
- PAUL, J. R. and TRASK, J. D. A comparative study of recently isolated human strains and a passage strain of poliomyelitis virus. *J. Exper. Med.*, 58: 513-529, 1933.
- TRASK, J. D., PAUL, J. R., BEEBE, A. R. and GERMAN, W. J. Viruses of poliomyelitis: an immunological comparison of 6 strains. *J. Exper. Med.*, 65: 687-704, 1937.
- KESSEL, J. F., STIMPET, F. D. and FISK, R. T. Immunologic comparison of a Los Angeles strain of poliomyelitis virus with the MV strain. *Am. J. Hyg.*, 27: 519-529, 1938.
- KESSEL, J. F. and STIMPET, F. D. Immunity in monkeys recovered from paralytic attacks of poliomyelitis. *J. Immunol.*, 40: 61-72, 1941.
- HOWE, H. A. The epidemiology of poliomyelitis. *Am. J. Med.*, 6: 537, 1949.
- TURNER, T. B., YOUNG, L. E. and MAXWELL, E. S. The mouse-adapted Lansing strain of poliomyelitis virus. iv. Neutralizing antibodies in the serum of healthy children. *Am. J. Hyg.*, 42: 119-128, 1945.
- BELL, E. J. The relationship between the anti-poliomyelitic properties of human naso-pharyn-

- geal secretions and blood serums. *Am. J. Hyg.*, 47: 351-369, 1948.
24. PEARSON, H. E. and BROWN, G. C. Recovery of virus from throats of poliomyelitis patients. *Proc. Soc. Exper. Biol. & Med.*, 66: 503-505, 1947.
 25. HOWE, H. A. and BODIAN, D. Isolation of poliomyelitis virus from the throats of symptomless children. *Am. J. Hyg.*, 45: 219-222, 1947.
 26. HOWE, H. A. and BODIAN, D. Passive immunity to poliomyelitis in the chimpanzee. *J. Exper. Med.*, 81: 247-254, 1945.
 27. BAHLKE, A. M. and PERKINS, J. E. Treatment of preparalytic poliomyelitis with gamma globulin. *J. A. M. A.*, 129: 1146, 1945.
 28. FISCHER, A. E. and STILLERMAN, M. Does an attack of acute anterior poliomyelitis confer adequate immunity? *J. A. M. A.*, 110: 569-572, 1938.
 29. HAMMON, W. McD. and ROBERTS, E. C. Serum neutralizing antibodies to the infecting strain of virus in poliomyelitis patients. *Proc. Soc. Exper. Biol. & Med.*, 69: 256-258, 1948.
 30. LANDSTEINER, K. Poliomyélite antérieure aiguë chez le singe. *Semaine méd.*, 28: 620, 1908.

Histopathologic Basis of Clinical Findings in Poliomyelitis*

DAVID BODIAN, M.D.

Baltimore, Maryland

THE purpose of this account is to consider the present status of knowledge of those aspects of the pathology of poliomyelitis which concern the clinician. If he is to establish an early diagnosis and initiate such therapy as will afford the patient a maximum opportunity for recovery, he must interpret the extremely variable clinical picture in terms of the underlying infectious process. Predominantly this involves a reaction in the tissues of the central nervous system, to which this discussion will be restricted. It is a remarkable fact that even in those non-nervous tissues from which the virus of poliomyelitis may be isolated at autopsy, its effect is so subtle that as yet it cannot be demonstrated by histologic means. Yet, so widespread is the influence of neurophysiologic mechanisms in the body and so far-reaching the effects of the virus within the nervous system, that the symptomatic picture of the disease involves the alteration of function of many body structures and is notoriously variable in character as well as in severity. With regard to the point of view to be presented in this account it should be mentioned that the data upon which it is based were obtained from detailed study of the central nervous systems (CNS) of twenty-four human autopsy cases^{1,2} and from studies of experimental poliomyelitis in monkeys.³⁻⁷

DEVELOPMENT OF THE HISTOPATHOLOGIC REACTION

A satisfactory correlation of symptoms and of pathologic substrate depends on a clear understanding of the sequence of

cellular changes throughout the disease. Naturally, the earliest changes are most informative. Several facts revealed by experimental work are important for understanding the origin of the histopathologic reaction. The first is that virus activity cannot be detected in the CNS until microscopic lesions are apparent.^{6,8} The second is that the onset of virus multiplication in the CNS and of the cellular pathologic reaction precedes the onset of paralysis by at least one day, and often several days. The earliest visible changes in an infected region in the spinal cord are first, chromatolysis of Nissl substance in the cytoplasm of some of the nerve cells and, second, very mild inflammatory changes. These consist of the appearance of polymorphonuclear and mononuclear cells, initially in the perivascular region and soon thereafter diffusely in the gray matter. In later stages, such as are represented in human autopsy material, the inflammatory changes become widespread and obscure these important early details.

It is interesting that although the injury and destruction of nerve cells may be independent of inflammatory changes, the latter do not occur in the absence of nerve cells. For example, in regions of the thalamus deprived of nerve cells by means of retrograde degeneration following ablation of the cerebral cortex, the inflammatory changes of poliomyelitis do not occur even when virus is introduced directly into such areas. This suggests that although the inflammatory reaction as it develops may be complexly determined, its origin, at least, is

* From the Poliomyelitis Research Center, Department of Epidemiology, Johns Hopkins University, Baltimore, Md. Aided by a grant from The National Foundation for Infantile Paralysis, Inc.

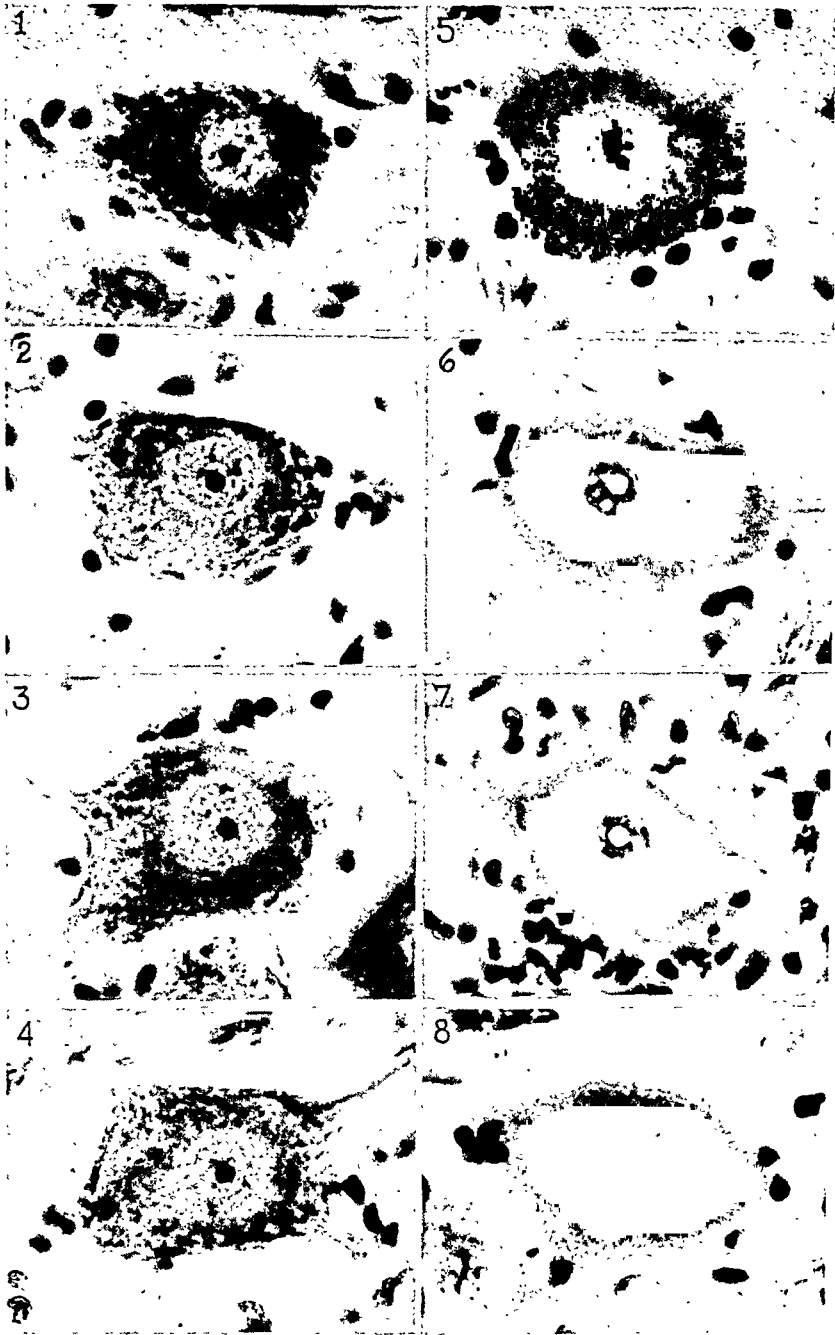


FIG. 1. Regressive stages in spinal cord motoneurons in poliomyelitis. Rhesus B₁₂ first day of paralysis. (1) Normal anterior horn cell. Note massive Nissl bodies in cytoplasm, central position of nucleus, large nucleolus and dispersed chromatin; (2 to 4) early regressive stages. Note diffuse decrease in size of Nissl bodies (chromatolysis) and nucleus essentially normal; (5) severe diffuse chromatolysis, with only a few small masses of Nissl substance in cell periphery. Note clumping of chromatin in nucleus; (6) complete dissolution of Nissl bodies in cytoplasm which is slightly basophilic in staining. Nucleus is slightly shrunk and contains a small eosinophilic inclusion body; (7) cell similar to that in 6, with further shrinkage of nucleus. Note infiltrating "polyblasts" surrounding the nerve cell; (8) completely chromatolytic cell with severe diffuse basophilia of cytoplasm and of shrunk, distorted nucleus.

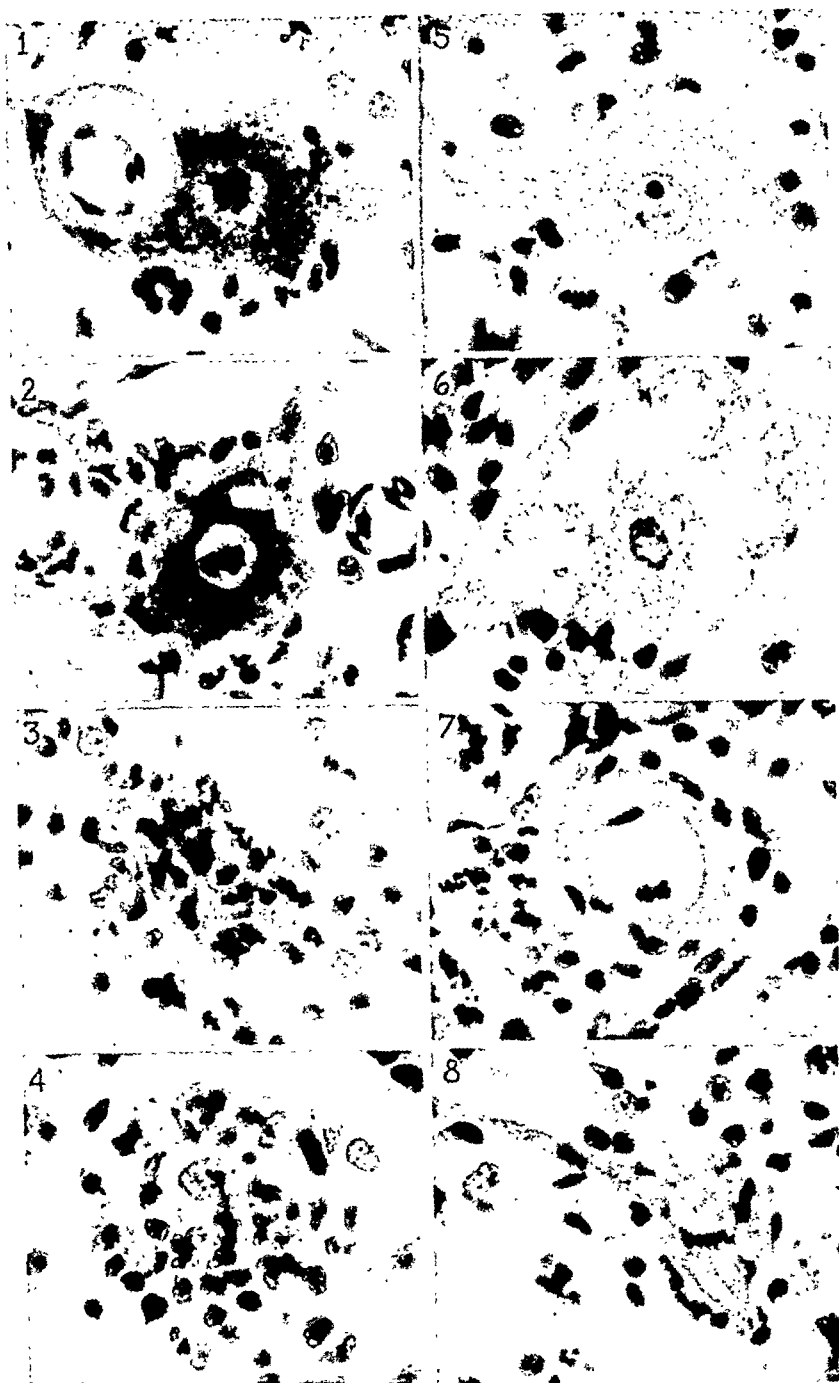


FIG. 2. Stages of degeneration of motoneurons during first day of paralysis, showing destruction by phagocytosis (1 to 4), by cytolysis (5 and 6) and by vacuolation with absorption (7 and 8); 1, 2, 3, 5, 7 and 8 from rhesus B₁₂; 4 and 6 from rhesus A696. (1) Intensely hyperchromatic cytoplasm and shrunken nucleus. Such basophilic cells are more commonly phagocytized than those which become acidophilic. Note blood capillary enclosed by cytoplasm of cell; (2) shrunken, hyperchromatic cell with granular and vacuolated cytoplasm and pyknotic nucleus. Beginning neuronophagia by surrounding leukocytes and macrophages; (3) active neuronophagia of necrotic cell; (4) macrophages and glia cells at site of a completely phagocytized cell; (5) complete chromatolysis, with no trace of basophilia in the cytoplasm. Such cells appear to be on the verge of "acidophilic necrosis" or the cytolysis and vacuolation shown in 6 to 8; (6) cytolysis of cell with shrunken nucleus showing a beaded, basophilic border. After complete cytolysis a punched-out, fluid-filled cavity is left ("falling out") which is reduced in a short time by shrinkage and the infiltration of macrophages, etc.; (7 and 8) cells in final stages of vacuolation, with surrounding and invading phagocytic cells.

dependent upon a specific reaction of the virus with nerve cells.⁴

The changes in nerve cells may occur with extraordinary rapidity so that some motor nerve cells are destroyed in the pre-paralytic period. The sequence of changes leading to destruction is summarized in the accompanying photomicrographs of cells found in the pre-paralytic and early paralytic stage in rhesus monkeys. (Figs. 1 and 2.) Many cells pass through most of these stages without evidence of surrounding inflammatory cells or exudate. It is evident that dissolution of the cytoplasmic Nissl substance is the earliest visible change and that as this progresses changes in the nucleus begin. When irreversible changes have occurred, the necrotic cell may be removed by neuronophagia due to leukocytes or macrophages, or may undergo lysis. (Fig. 2.)

The changes in nerve cells in the acute stage are accompanied by an increase of inflammatory cells which soon may reach tremendous proportions. Three principal types of such cells are found in the earliest stage, polymorphonuclear leukocytes, microglia (polyblasts, macrophages) and mononuclear leukocytes. The polymorphonuclear cells may be extraordinarily numerous in some cases but persist only for a few days. The microglia are active macrophages during the acute stage but persist in modified forms for weeks. Mononuclear cells are predominantly lymphocytic cells and are present diffusely in the tissue for two or three weeks, but persist as perivascular accumulations for several months.

GENERAL PATHOLOGIC FACTORS AFFECTING THE CLINICAL PICTURE

The signs and symptoms of poliomyelitis may vary from a few mild and transient manifestations to a great assortment of abnormalities due both to localized lesions in the CNS and to the unlocalized affects of an acute infection of the CNS. The clinical picture may therefore combine the features of an exceedingly complex and varied neurologic disease and those of a severe inflammatory process. Added to this

one may have the baffling effect of a process in which recoverable injury of many nerve cells may be combined with irreversible injury to many others, in many different proportions. The principal reason for the great variability of the signs and symptoms of poliomyelitis is not the variation in the localization of lesions in the CNS but rather the variation in severity of nerve cell injury and inflammatory response in different centers. Experimental work suggests three possible factors which may determine the variation in severity of infection.⁷ These are, first, variations due to differences in strains of the virus, second, reduction of severity due to previous paralytic or non-paralytic infection⁹ and, third, host variation unrelated to previous immunizing experience with the virus. Although second attacks of paralytic poliomyelitis are infrequent events and apparently due to re-infection with strains of different immunologic types,⁹ the known existence of at least three of such immunologic types²⁰ makes it probable that paralytic attacks may be rendered mild due to previous unrecognized infection with virus of a different immunologic type.

It is important to emphasize moreover that although lesions appear in certain functional centers in the CNS, symptoms attributable to such injury need not necessarily result. Such injury must reach a certain threshold of severity, varying with the margin of safety of each center before a clinical effect is observed. The evidence from experimental work and from human material is overwhelmingly clear on this point. Neuronal and inflammatory lesions may be regularly found in any susceptible center, including the anterior horn of the spinal cord, in individuals who have never exhibited symptoms which are known to follow massive injury to such centers. In experimental primates neuronal and inflammatory lesions may indeed be found in all susceptible centers in the CNS in animals who have had inapparent infections.⁵ The obvious explanation of this is that severe lesions are usually necessary to

produce dysfunction at the clinical level and one must therefore look for centers which are severely involved for the site of origin of clinical signs.

EFFECTS OF THE INFLAMMATORY REACTION

Severe inflammatory reactions in poliomyelitis are usually but not always associated with extensive nerve cell destruction. (Fig. 3.) In some cases the inflammatory response in small areas may be enormous and associated at times with a small focus of tissue softening. Occasionally a small vessel in such an area may rupture, producing a petechial hemorrhage. These softenings were clearly described by Harbitz and Scheel¹⁰ and occur only in the severest infections. Such softenings are never numerous, are rarely larger than 1 or 2 mm. in size and are not the result of vascular emboli. It is not clear whether they are the result or the cause of the very dense cellular infiltration with which they are always associated. It seems doubtful that nerve cell injury or destruction alone is responsible for such an unusual reaction since in many areas of severe nerve cell destruction the inflammatory response is relatively quite mild. It may be that local ischemia can result from the agglutination of circulating blood described by Knisely, et al.^{10a} in acute cases, perhaps accentuated by the increased demand for oxygen in some severely affected areas. Since tissue rarefaction or softening occurs only in those regions which contain the specific lesions of poliomyelitis, it is apparent that local ischemia alone cannot be the cause. Perhaps the combination of severe reaction to virus and local circulatory embarrassment is responsible not only for the occasional focal rarefactions, petechial hemorrhages and softenings seen in poliomyelitis, but also those frequently described in other viral encephalitides. It is also conceivable that in small areas an unusually high concentration of virus may produce a toxic effect apart from the ordinary pathologic effect of virus multiplication in the nerve cells. Such toxic effects of influenza virus



FIG. 3. Photomicrographs of human spinal cords, showing that the usual association of severe inflammatory lesions with extensive nerve cell destruction does not always occur. Gallocyanin stain, $\times 30$. (1) Severe motoneuron loss in posterior part of anterior horn with very slight inflammatory reaction (Case H37, lumbar cord three days after onset of illness); (2) severe focal, diffuse and perivascular infiltrations of lymphocytes and histiocytes, with most anterior horn cells relatively intact in appearance (Case H34, lumbar cord twelve days after onset of illness).

have been described for example by the Henle's.^{16b} These speculations simply indicate our ignorance of many of the intimate details of cellular pathologic reactions. At any rate, the focal tissue breakdown is not a primary factor in producing the paralysis of poliomyelitis since it follows the period of greatest nerve cell damage and occurs in scattered foci even in the severest cases. If it occurred more commonly in patients or more extensively in the CNS, one would hardly expect to see the high degree of recovery of function which occurs.

We have seen no evidence in our material,

experimental or human, that edema plays a dominant role in the production of paralysis, as suggested by Wickman¹¹ and frequently stated. Whenever a severe inflammatory response occurs in a cord segment, the cord in such an area may show

human cases show no such severity of inflammatory reaction indicates that it need not be assumed to be a regular feature of the disease and certainly not in non-fatal infections. Moreover, severe paralysis may occur without evidence of edema and, in

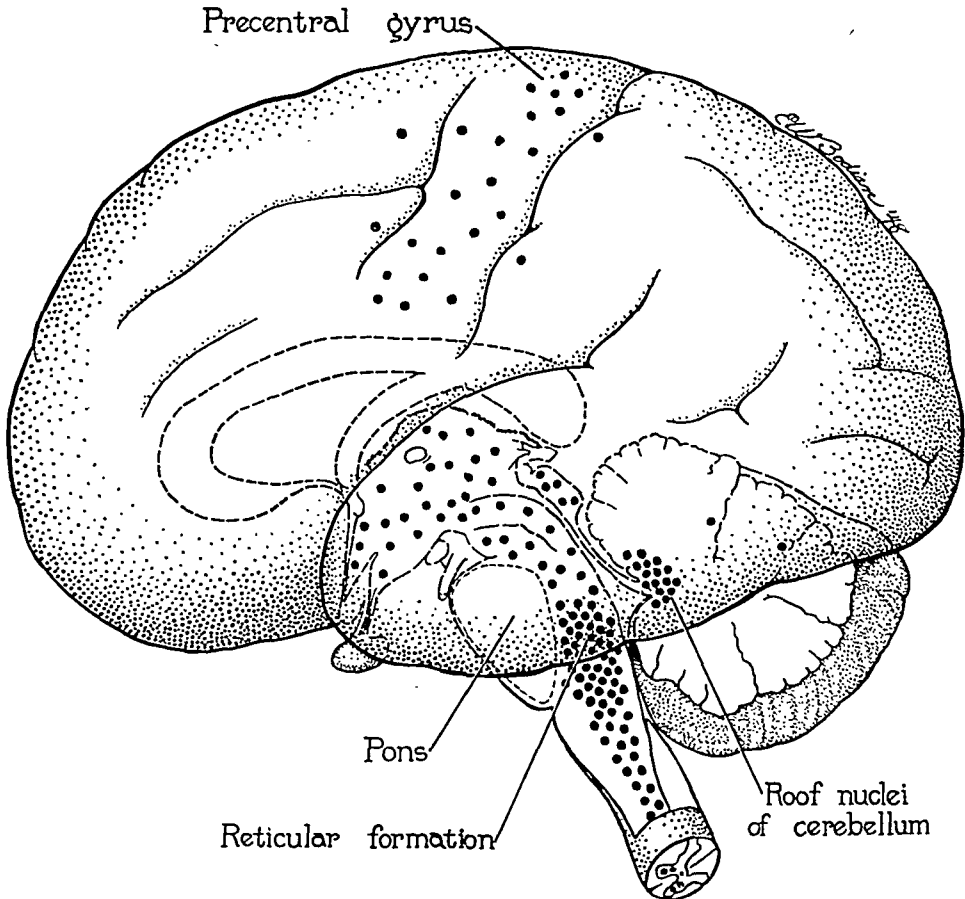


FIG. 4. Lateral view of human brain, with schematic transparent projection of the mid-sagittal surface of the brainstem. General distribution of lesions of poliomyelitis is indicated by large dots. Lesions in the cerebral cortex are largely restricted to the precentral gyrus and those in the cerebellum to the roof nuclei. Lesions are generally found widespread in the brainstem centers, with a number of striking exceptions such as the nuclei of the basis pontis and the inferior olivary nuclei.

swelling of the freshly cut surface. In our experience, however, an inflammatory response severe enough to produce massive exudate in the anterior gray columns usually occurs after most of the anterior horn cells in the region are already destroyed by virus action. In such cases there can be no question of possible recovery from paralysis since all or most of the motoneurons are destroyed. This occurs in monkeys with severe paralysis and in many fatal human infections. The fact that other fatal

some cases, without important vascular changes or severe leukocytic infiltration in the cord.

DISTRIBUTION OF LESIONS

It is now well known that virus activity, nerve cell changes and inflammatory reaction are localized only in certain regions of the CNS. It has been apparent since the classical study of Harbitz and Scheel¹⁰ that lesions of the brain are invariably found in fatal infections. In experimental animals

this includes non-paralytic as well as paralytic infections. As far as the pathologist is concerned all cases of poliomyelitis are "encephalitic." However, it is important to note that some parts of the brain rarely if ever are affected, and only certain centers are severely involved often enough to suggest that their injury produces symptoms. The regions which rarely if ever are affected include primarily the entire cerebral cortex, except for the motor area, the corpus striatum, except occasionally for the globus pallidus, the cerebellar cortex except for the vermis, and the base of the pons. In other words, the brainstem as far forward as the hypothalamus and thalamus bears the brunt of the cerebral pathologic changes in poliomyelitis and lesions in the cortex are largely confined to the motor cortex. (Fig. 4.) The characteristic distribution of poliomyelitis lesions has been shown experimentally to be due to two principal factors: first, the inherent resistance of some nervous centers to infection and, second, the restricted movement of virus along certain nerve fiber pathways.³

Lesions in the Cerebral Cortex. An interesting aspect of the pathology of poliomyelitis, as compared with some other virus encephalitides, is that the cerebral cortex which makes up the largest proportion of the brain substance rarely shows any pathologic changes except in the motor area of the precentral gyrus. (Fig. 5, part 1.) Even the lesions here are rarely severe and it is doubtful that they are sufficiently intense to produce clinical signs, except perhaps in rare instances. This point has been so thoroughly documented since the report of Harbitz and Scheel¹⁰ that it is unnecessary to elaborate upon the evidence here. It has been reviewed in detail elsewhere.^{1,2}

The relatively slight involvement of cerebral cortex indicates that residual behavior disturbances, as well as spastic phenomena in poliomyelitis, cannot be the result of specific lesions in the cerebral cortex. Moreover, other so-called "encephalitic" symptoms, including restless-



FIG. 5. Cerebral cortex and hypothalamus of a human (Case H12) nine days after onset of severe paralytic poliomyelitis. Galloxyanin stain. (1) Precentral gyrus (right) and postcentral gyrus (left) showing remarkable localization of lesions in precentral (motor) cortex only. Lesions of greater severity are rare in fatal cases and it is doubtful that they contribute significantly to the clinical picture. ($\times 5$) (2) Hypothalamus at level of paraventricular nucleus (below) showing severe perivascular and focal infiltrative lesions. Such lesions as well as neuronal lesions are common in fatal cases. ($\times 20$)

ness, drowsiness, disorientation and coma, which occurred in some of our cases were not associated with heavier than usual reaction in the cerebral cortex but rather with a greater intensity of inflammatory reaction in the brainstem, extending as far forward as the hypothalamus. (Fig. 5, Part 2.) It has recently been suggested that some of these symptoms may be due to hypoxia rather than to specific brain lesions.¹² If this is the case, there is never-



FIG. 6. The reticular formation and vestibulocerebellar centers in poliomyelitis. Galloxyanin stain. (1) Case H32 five days after onset of disease. Extensive nerve cell destruction and inflammatory reaction in reticular formation, vestibular nuclei (left) and roof nuclei of cerebellum (above fourth ventricle). Very little involvement of dentate nucleus of cerebellum (upper right). ($\times 10$.) (2) Case H12 nine days after onset of disease. Lesions are the same as in 1 but are especially severe in the left vestibular nuclei and in the right cerebellar roof nucleus. ($\times 5$.)

theless a correlation between "encephalitic" symptoms and severe brainstem involvement although the association may prove to be an indirect one.

Lesions in Brainstem Centers. Lesions in brainstem centers have long been recognized as being associated with fatal poliomyelitis infections^{10,11} and with poliomyelitis infections in which death was not due to this disease.^{1,2,3,5,13,14} The association of severe lesions in cranial nerve nuclei with paralysis of corresponding muscles is, of course, well known and obvious. What is less well

recognized, however, is that most of the brainstem centers, with some outstanding exceptions such as the nuclei of the basis pontis and the inferior olives, may be severely affected in poliomyelitis. Moreover, in our series of twenty-four human autopsies there was hardly an individual who did not have lesions, sometimes of a fairly severe degree, in most of the motor nuclei of the cranial nerves as well as in the surrounding reticular formation.¹ Yet clinical signs of paralysis in the corresponding muscles were rarely recorded, except in the face, pharynx and larynx in bulbar cases. The remaining nerve cells in oculomotor, motor trigeminal and hypoglossal nuclei are generally adequate to maintain good clinical function, even in many severe bulbar infections. This illustrates the margin of safety of these centers, and perhaps also a tendency on the part of the clinical examiner to overlook mild weakness of some of the cranial nerve musculature.

The three centers in the brain most often severely affected are the reticular formation, the vestibular nuclei and the roof nuclei of the cerebellum. (Fig. 6.) The severe and extensive involvement of the former has often been recorded.^{1,2,11,15,16,17} In view of the fact that a number of vital functional centers are located in the reticular formation, it is surprising, in a sense, that a fatal termination is not more common. Although material from fatal bulbar infections reveals destructive changes in the reticular formation in maximal degree, some of our material from patients who had no bulbar signs and who died of paralysis of respiratory muscles or of complications unrelated to poliomyelitis infection also showed severe lesions in this region. Rarely, brainstem damage was minimal although cord involvement was severe. (Fig. 7.) A similar case was described by Barnhart et al.¹⁶

In recent years certain complex functions of the brainstem have been localized in the reticular formation although not in as sharply delimited areas as those containing the cranial nerve nuclei. Experimental

evidence regarding the localization of respiratory, vasomotor, swallowing and motor inhibitory mechanisms has been reviewed by Barnhart et al.¹⁶ Disturbances of these functions are no doubt correlated in many instances with the extensive lesions observed in the reticular formation. Guizetti, in emphasizing the presence of lesions in the reticular formation, suggests a possible role of such lesions in producing autonomic dysfunction.¹⁵ Evidence has recently been presented that generalized spasticity in the preparalytic stage of poliomyelitis in rhesus monkeys may be due to lesions of the reticular formation¹⁸ involving the bulbar inhibitory mechanism described by Magoun and Rhines.¹⁹ An attempt to make a more precise correlation of respiratory and cardiovascular symptomatology in bulbar infections with poliomyelitic destruction of restricted areas of the reticular formation has been made by Brown, Baker and McQuarrie¹² (and *Am. J. Med.*, 6: 614, 1949). Large symmetrical lesions of the type they observed have not been described by others so that it remains to be seen how frequently discrete destructive lesions occur which are large enough to destroy functions apparently diffusely represented in the reticular formation. In most of our material and that described by others the lesions in the reticular formation in fatal bulbar cases were heavily peppered throughout this region rather than being predominantly composed of large discrete areas of destruction. In a few instances clearly delimited areas of complete neuron destruction were seen, as large as 1 or 3 mm. in diameter. Two of these cases have been described in detail before.² In one in which such lesions were in the lateral reticular formation in the region of the nucleus ambiguus on both sides death was due to respiratory failure. In another with similarly placed lesions, death during convalescence was due to acute appendicitis and no respiratory difficulty had previously been noted. There are thus serious limitations in the classification of bulbar cases according to the site of predominant destruction in the reticular



FIG. 7. Unusual case of fatal spinal paralysis with little brainstem involvement. H40 seventeen days after onset of disease. Gallocyenin stain. (1) Section of lumbar cord showing complete motoneuron destruction and massive inflammatory reaction, especially on the left side. Note the heavy perivascular infiltrations characteristic of the subacute and early convalescent periods. ($\times 20$.) (2) Same case as in 1 showing relatively slight involvement of the medulla oblongata. ($\times 10$.)

formation, as attempted by Brown et al.¹² Indeed, these authors emphasize the well known overlap of signs and symptoms in bulbar infections. The reason for this overlap is apparent in the widespread distribution of lesions in the brain stem in all fatal bulbar infections.

At the present time it is not possible to assign clinical symptoms to the regularly severe damage of the vestibular nuclei until experimental work has shown the effect both of isolated lesions in these centers and of such lesions in conjunction with injury to the reticular formation, the roof nuclei of the cerebellum, or both. These three centers are interconnected by fiber

tracts and there is increasing evidence that they are concerned with the modification of motor activities originating in the cerebral cortex. Severe lesions in the roof nuclei of the cerebellum are fairly common in monkey and in human poliomyelitis but, although monkeys often show severe tremor in the preparalytic and acute stage, occasionally with ataxia, these symptoms apparently are relatively uncommon in human cases. When ataxia does occur in human cases, it is probably due to severe damage to the deep cerebellar nuclei. The cortex of the cerebellum is almost always free of lesions, except for scattered foci in the vermis. It is conceivable that the margin of safety of vestibular centers and of the cerebellum is great enough to preclude the occurrence of symptoms when the injury is not too massive. It is also conceivable that the nausea and vomiting seen in some cases is due to severe lesions in the vestibular region. Vertigo and nystagmus have rarely been described in spite of the frequent occurrence of severe vestibular and cerebellar lesions.

Relation of Spinal Lesions to Paralysis. In the spinal cord, as is well known, the severest lesions are always in the anterior columns. With severe cord involvement intermediate horns may also be heavily damaged and posterior horns moderately affected, but such damage is more spotty in distribution than in the anterior horns and the posterior and intermediate columns are never wiped out over whole segments as are the anterior columns at times. It is to be expected, then, that when internuncial neurons in the intermediate columns are severely affected, the neighboring anterior columns of the cord are so extremely damaged that flaccid paralysis is likely to be the only symptom referable to this region of the cord. The possibility remains, however, that internuncial neuron damage in the cord may contribute to the motor dysfunction of muscles not completely paralyzed.

An important finding in quantitative studies of experimental poliomyelitis is that most motor nerve cells in the spinal cord enlargements show morphologic evidence

of virus invasion in paralytic individuals, regardless of whether the paralysis is mild or severe.⁷ Since mild chromatolysis is the only sign of such invasion in many cells and can be clearly demonstrated only in well fixed material, this generalized invasion of most motor nerve cells in the spinal cord enlargements could not be confirmed in our human material. It is possible that the much larger size of the human cord is a deterrent to such widespread involvement of the spinal cord as occurs in monkeys. A few of our cases in which death occurred soon after onset appeared to have minimal lesions in the lumbar cord in the presence of severe involvement of the cervical cord. The reverse also occurred. In mild experimental cases in the first days of the disease the great majority of cells exhibit a mild degree of diffuse chromatolysis of cytoplasmic Nissl substance. In the presence of slight weakness of the muscles innervated by such cells it is clear that neurons in this state are still functional. Quantitative evidence strongly suggests that the function of infected motor nerve cells disappears only in the stage of severe chromatolysis. The widespread dissemination of virus among the motor nerve cell population occurs as early as the first day of paralysis. Motor nerve cells which are affected either are destroyed very quickly during the first few days of the disease or undergo slower recovery changes leading to complete morphologic recovery within about a month. In limbs showing complete paralysis recovery is, of course, rare and in such cases it can easily be shown that only about 10 per cent of the motoneurons, or less, have survived. Experimental material clearly shows that the degree of nerve cell destruction alone can account for most of the paralysis in the subacute and early convalescent period, and is also correlated with the degree of muscle atrophy. In the acute stage the correlation between nerve cell destruction and paralysis is not quite so high so that apparently other factors also play a role in producing paralysis. One of the most significant appears to be the

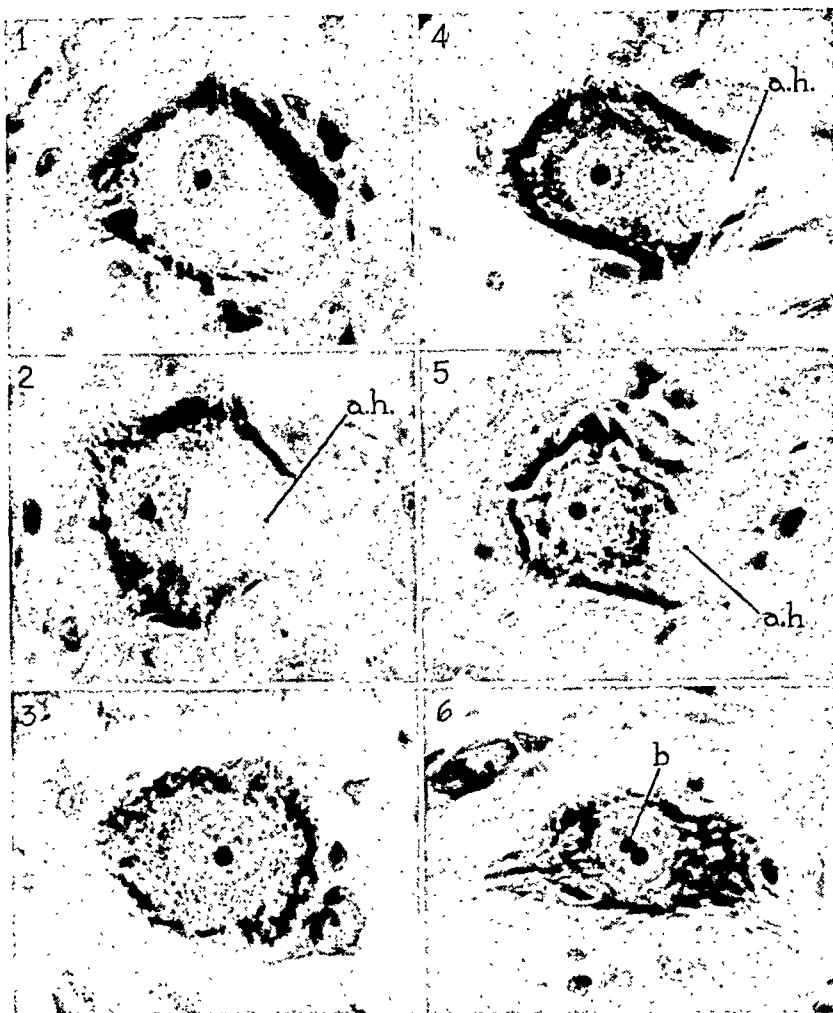


FIG. 8. Rhesus B32. Ninth day after onset of paralysis. (1) Severe central chromatolysis, with normal-appearing nucleus and accumulation of heavy masses of Nissl substance near the cell membrane. Regeneration of Nissl substance may or may not occur near the nuclear membrane; (2 to 5) similar cells but with small Nissl bodies in the central area. This appearance suggests regeneration of Nissl bodies from the periphery inward, with the area around the axon hillock (ah) last to show recovery (2, 4 and 5); (6) motoneuron of essentially normal appearance except for presence of acidophilic inclusion body (b) in nucleus. In the acute stage such inclusion bodies are seen only in cells with severe chromatolysis, suggesting almost complete recovery of such a cell.

injury of nerve cells to a degree incompatible with function but not with recovery. In all instances in which paralysis is not complete the reversible injury of many motor nerve cells by virus activity must be very common.⁷ Although available human material is not adequate for this type of study, the material which we have examined and the few cases in the literature in which nerve cell changes are dealt with indicate that a similar process occurs in human poliomyelitis. In all of our human

cases with a duration of disease longer than three days active neuronophagia was no longer common. In most instances evidence of active destruction of nerve cells, present in earlier cases, was absent. It is obvious that reported failures to find neuronophagia are due to the belated arrival of the observer. Within a few days after onset almost the entire degenerative phase of motor nerve cells may be terminated and the virus concentration, previously high, falls abruptly. Most remaining cells after

the early acute stage show a pattern of cytoplasmic Nissl substance quite different from the diffuse chromatolysis of this period. The remaining Nissl substance instead tends to aggregate in heavy masses near the nerve cell membrane, leaving a pale-

in nerve cells and in virus concentration in the acute and subacute periods are summarized in Figure 9.

In experimental as in human cases, anterior horn cells may be destroyed either in large groups or in scattered fashion over

ASSOCIATION OF PATHOLOGICAL STAGES IN MOTONEURONS
WITH SPINAL VIRUS LEVELS

PREDOMINANT STAGES IN MOTONEURON DESTRUCTION



PREDOMINANT STAGES IN MOTONEURON RECOVERY

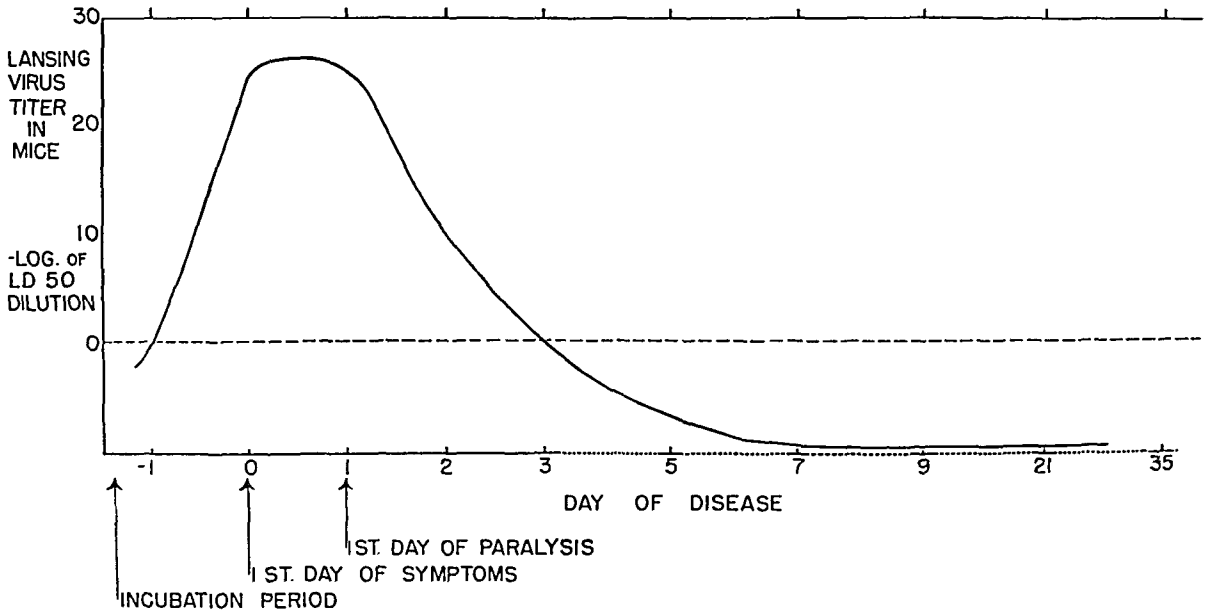


FIG. 9. Schematic representation of sequence of cytopathologic stages in motoneurons in the course of destruction and those chromatolyzed but able to recover. The approximate time course of changes is shown, with a parallel curve showing the trend of rise and decline of virus concentration in the rhesus spinal cord (from Bodian and Cumberland, 1947). Note that peak levels of virus concentration are attained at the time when the predominant stage of cell change in the motoneuron population is that of diffuse cytoplasmic chromatolysis. The curve is a partly hypothetical one, showing Lansing virus activity in the rhesus spinal cord. The curve up to the third day of paralysis is based on median values of several specimens of infected monkey cord taken at each time period and titrated in mice. The decline beyond the third day of paralysis is shown in a speculative way and is based on the decreasing probability of obtaining virus in concentrations infective by monkey passage.

staining central area in the center of the cell body. This appearance of central chromatolysis is characteristic of the recovery stages of nerve cells and has been shown by quantitative studies in monkeys to lead to complete morphologic recovery of most cells during the subacute stage of the disease. (Fig. 8.) The parallel changes

a period of only a few days. Motor nerve fibers begin to degenerate about three days after destruction of the nerve cell body and show the typical morphologic changes as well as the time course of Wallerian degeneration. The resulting muscle atrophy follows the time course seen, for example, in Wallerian degeneration due to nerve

section, and in cases of severe paralysis is apparent within two weeks after onset of paralysis.

OTHER SYMPTOMS AND SIGNS POSSIBLY OF BRAINSTEM OR SPINAL CORD ORIGIN

Since lesions sometimes severe are found in the posterior and intermediate horns of the spinal cord as well as in the spinal ganglia, it is possible that spinal internuncial discharge pathways and reflex pathways may be injured sufficiently to contribute to motor dysfunction. Recovery of such mechanisms probably follows a course similar to that in the brainstem centers since the two are intimately connected by ascending and descending pathways.

Symptoms in addition to paralysis which are often recorded are muscle pain, hyperesthesia and stiff neck and back. Occasionally paresthesias occur. Our material can offer no more than a confirmation of earlier findings of mild exudate in meninges and lesions of varying degrees of severity in spinal ganglia, posterior columns of the spinal cord and thalamus to account conceivably for these symptoms. In view of the rather slight involvement of these areas in many cases interpretations must be tentative. The common symptoms of neck and back stiffness are usually interpreted as being due to "meningeal irritation" but it is possible that they are the result of the same brainstem disturbances which give rise to other phenomena of spasticity in poliomyelitis. This is suggested by the frequently occurring pattern of hypertonia in postural muscles in human poliomyelitis. The frequent association of muscle pain with paralysis in the same limb suggests that this pain is the result of lesions in the posterior columns of the spinal cord or perhaps in the spinal ganglia. Lesions are found in these regions especially in segments in which severe involvement of the anterior motor columns of the spinal cord has occurred. The occasional association of pain and paralysis in the same limb does not therefore require a postulate of peripheral origin of pain in paralyzed muscles,

especially since many paralyzed muscles never exhibit either pain or tenderness.

Since lesions in the cerebral cortex are largely confined to the precentral gyrus and since lesions in the sympathetic ganglia were not present in the human cases we have studied, symptoms referable to the autonomic system are very likely the result of central lesions in the brainstem or spinal cord, or both. In some cases lesions in the hypothalamus may be severe (Fig. 5, part 2) and in other cases negligible in amount. Similarly, one occasionally finds severe destruction of cells in the sympathetic motor columns of the spinal cord although this is uncommon and always restricted in extent. In contrast, lesions in the central gray of the mid-brain and hind-brain and in the mid-brain tegmentum and reticular formation are very common and often severe. It is conceivable that such lesions are responsible for vasomotor changes and other dysfunctions of the autonomic system occasionally reported in poliomyelitis. It is probable that symptoms of autonomic dysfunction would be more often observed if they were not overshadowed by the more serious symptoms of paralysis of skeletal muscles.

FACTORS IN THE RECOVERY OF MOTOR FUNCTION

Although any discussion of recovery factors must necessarily be speculative in part at this time, even a speculative analysis from the point of view of histopathology may be helpful in identifying the parts of the neuromotor apparatus which must be considered. As already stated, the cerebral cortex is so little affected by the disease process that there is every reason to suppose that the patient can rapidly begin to relearn patterns of motor activity which formerly were smoothly and subconsciously regulated by now severely damaged brainstem mechanisms.

Most of the brainstem centers concerned with motor functions are damaged in varying degree in poliomyelitis, yet an evaluation of recovery from this damage

must be phrased in very general terms until the precise contribution of each center in motor functions is better understood. It is difficult to believe that the brainstem damage does not affect motor performance even in some mild paralytic cases since such instances in experimental animals and one of our human poliomyelitis cases succumbing after fifteen days as a result of acute appendicitis (H9) showed considerable neuron destruction and infiltrative lesions in some brainstem centers, especially the vestibular nuclei and reticular formation. Recovery from such lesions should result from at least two processes, the first recovery of neurons not damaged sufficiently to be destroyed and, secondly, the re-routing of neuron-chain discharge pathways from interrupted primary paths to secondary alternative paths. The first process is probably completed in about one month, as is the case in the spinal cord, whereas the second process probably is of longer duration since it is a part of the relearning process.

In further assessing the pathologic factors which underlie the paralysis in poliomyelitis it is important to keep in mind evidence showing that reversible changes may occur in spinal motoneurons in the acute stage.⁷ This means that a probably important component of muscle weakness in the acute stage may be a partial and temporary loss of function of some motor units, as contrasted with the more common occurrence of irreversible loss of function of a varying number of denervated muscle fibers due to motoneuron destruction. In fact, it seems reasonably certain from experimental data that the pathologic and recovery changes in motor nerve cells alone can account for much of the paralysis and its early recovery, respectively. The other factors mentioned probably play a secondary role although the possibility cannot be excluded that in special cases they may be more important. The slow but sometimes significant increase of power in paralyzed limbs after the third month has not been studied in detail by us because of the small numbers

of cases available. Since the morphologic and probably functional status of the nervous system does not change significantly after the first and second months, such recovery as occurs after this time is probably the result of slower compensatory hypertrophy of muscle fibers with intact innervation. In our human material the entire spinal cord was available in one case surviving longer than two weeks (H40). In this case in which destruction of anterior horn cells was extensive throughout all levels, over 90 per cent of the surviving motoneurons were normal in appearance and most of the others were only moderately chromatolytic.

SUMMARY

1. Experimental evidence indicates that the onset of CNS pathologic changes occurs in the preparalytic period and is closely associated with the earliest evidence of virus activity in any particular region involved.

2. The earliest cytopathologic changes are diffuse chromatolysis of Nissl substance in the cytoplasm of nerve cells and mild cellular exudate consisting of polymorphonuclear and mononuclear leukocytes.

3. Nerve cell changes may be present in the earliest stages without inflammatory reaction in the vicinity and therefore are not necessarily the result of the latter, but rather the result of direct virus action.

4. Nerve cell changes either lead to rapid destruction of the cell or to arrest in the stage of cytoplasmic chromatolysis, following which complete morphologic recovery of the cell generally occurs over a period of about a month or less, depending upon the severity of injury.

5. Virus activity, nerve cell changes and inflammatory reaction are localized only in certain susceptible regions of the CNS, largely due to specific differences of susceptibility of nerve cells. The intensity of the inflammatory reaction, however, may be quite variable in different susceptible centers and in different individuals. Severe inflammatory reaction is usually but not

always associated with extensive nerve cell destruction. Severe nerve cell damage may occur without extensive cellular infiltration in the cord.

6. Lesions in the cerebral cortex are usually confined to the motor area of the precentral gyrus and even here the lesions are rarely severe enough to suggest that they may produce clinical symptoms.

7. "Encephalitic" symptoms such as restlessness, stupor, disorientation and coma are associated with severe inflammatory reaction in the brainstem and often with small softenings in this region. They are not associated with unusual involvement of the cerebral cortex.

8. Brainstem centers principally involved in most instances are the reticular formation of the hind-brain, the vestibular nuclei and the roof nuclei of the cerebellum. Resulting functional disturbances are discussed.

9. Widespread dissemination of virus among most motor nerve cells in spinal cord enlargements occurs in experimental poliomyelitis as early as the first day of paralysis. Motor nerve cells which are affected either are destroyed very quickly during the first few days of the disease or undergo slower recovery changes leading to complete morphologic recovery within about a month. After this time it can be shown that the degree of paralysis and atrophy are closely correlated with the number of motor nerve cells destroyed. In the acute stage, however, this correlation is not as high and other factors must also play a role in producing paralysis. An important factor is the reversible injury of motor nerve cells. Less complete evidence from human material suggests that a similar situation obtains in human poliomyelitis.

10. Experimental work suggests three possible factors which may determine the variation in severity of infection. These are, first, variations due to difference in strains of the virus, second, reduction of severity due to previous paralytic or non-paralytic infection, and third, host variation unrelated to previous immunizing experience with the virus.

The material upon which this article is based is described more fully in references 1 to 7, 14 and 18. The original illustrations of Figures 1, 2, 8 and 9 appeared in *Bull. Johns Hopkins Hosp.*, 68: 58, 1941 and those of Figures 3 to 7 in Poliomyelitis. Papers presented at the First International Poliomyelitis Conference. Philadelphia, 1949. J. B. Lippincott Co.

REFERENCES

1. BODIAN, D. Poliomyelitis. Neuropathologic observations in relation to motor symptoms. *J. A. M. A.*, 134: 1148, 1947.
2. HOWE, H. A. and BODIAN, D. Neuropathological evidence on the portal of entry problem in human poliomyelitis. *Bull. Johns Hopkins Hosp.*, 49: 183, 1941.
3. BODIAN, D. and HOWE, H. A. An experimental study of the role of neurones in the dissemination of poliomyelitis virus in the nervous system. *Brain*, 63: 135, 1940.
4. BODIAN, D. and HOWE, H. A. Neurotropism and the genesis of cerebral lesions in poliomyelitis: an experimental study. *Bull. Johns Hopkins Hosp.*, 68: 58, 1941.
5. BODIAN, D. and HOWE, H. A. Experimental non-paralytic poliomyelitis: frequency and range of pathological involvement. *Bull. Johns Hopkins Hosp.*, 76: 1, 1945.
6. BODIAN, D. and CUMBERLAND, M. C. The rise and decline of poliomyelitis virus levels in infected nervous tissue. *Am. J. Hyg.*, 45: 226, 1947.
7. BODIAN, D. The virus, the nerve cell, and paralysis: a study of experimental poliomyelitis in the spinal cord. *Bull. Johns Hopkins Hosp.*, 83: 1, 1948.
8. FAIRBROTHER, R. W. and HURST, E. W. The pathogenesis of and propagation of virus in experimental poliomyelitis. *J. Path. & Bact.*, 33: 17, 1930.
9. BODIAN, D. Differentiation of poliomyelitis viruses. 1. Reinfection experiments in monkeys (second attacks). *Am. J. Hyg.*, 49: 200, 1949.
10. HARBITZ, F. and SCHEEL, O. Pathologisch-anatomische Untersuchungen über akute Poliomyelitis und verwandte Krankheiten. Christiania, 1907. J. Dybwad.
- 10a. KNISELY, M. H., BLOCH, E. H., ELIOT, T. S. and WARNER, L. Sludged blood. *Science*, 106: 431-439, 1947.
- 10b. HENLE, G. and HENLE, W. Studies on the toxicity of influenza virus. 1. The effect of intracerebral injection of influenza viruses. *J. Exper. Med.*, 84: 623-637, 1946.
11. WICKMAN, I. Beiträge zur Kenntnis der Heine-Medinschen Krankheit. Berlin, 1907, Karger. English translation, Nerv. & Ment. Dis. Monograph Series, No. 16, 1913.
12. BROWN, J. R., BAKER, A. B., ADAMS, J. and MCQUARRIE, I. The bulbar form of poliomyelitis. *J. A. M. A.*, 134: 757, also 135: 425, 1947.
13. PEERS, J. H. The pathology of convalescent poliomyelitis in man. *Am. J. Path.*, 19: 673, 1943.
14. BODIAN, D. In Poliomyelitis. Papers presented at the

- First International Poliomyelitis Conference. Philadelphia, 1949. J. B. Lippincott Co.
15. GUIZETTI, H. U. Betrachtungen zur Poliomyelitis des Hirnstammes. *Deutsche Ztschr. f. Nervenh.*, 131: 29, 1933.
16. BARNHART, M., RHINES, R., McCARTER, J. C. and MAGOUN, H. W. Distribution of lesions of the brainstem in poliomyelitis. *Arch. Neurol. & Psychiat.*, 59: 368, 1948.
17. LUHAN, J. A. Epidemic poliomyelitis: some pathologic observations on human material. *Arch. Path.*, 42: 245, 1946.
18. BODIAN, D. Experimental evidence on the cerebral origin of muscle spasticity in acute poliomyelitis. *Proc. Soc. Exper. Biol. & Med.*, 61: 170, 1946.
19. MAGOUN, H. W. and RHINES, R. An inhibitory mechanism in the bulbar reticular formation. *J. Neurophysiol.*, 9: 165, 1946.
20. BODIAN, D., MORGAN, I. M. and HOWE, H. A. Differentiation of types of poliomyelitis viruses. III. The grouping of 14 strains into three basic immunological types. *Am. J. Hyg.*, 49: 234, 1949.

Problems of the Pathologic Physiology of Poliomyelitis*

FRITZ BUCHTHAL, M.D.

Copenhagen, Denmark

IN attempting to review the pathophysiology of an infectious disease which has an especial affinity for the central motor nervous system it is reasonable to limit the discussion to an analysis of the resulting neuromuscular disorders.

Such an analysis must, unfortunately, be limited since it demands a thorough knowledge of the normal physiology of motor function, a knowledge which is in many respects far from complete. In addition, utilization of material derived from clinical and pathologic research is often difficult due to the impossibility of controlling the conditions to a degree in any way comparable with a physiologic experiment, and only rarely can the complicated pathologic changes in the physiology be studied by direct experiment. Consequently, discussion becomes of necessity speculative and theories have to be modified repeatedly as further evidence accumulates.

In poliomyelitis, as in a number of other diseases, it has been of the utmost importance for the systematic study of its pathogenesis that analogous conditions be reproduced experimentally in animals and that manifestations of the disease be studied under controlled experimental conditions.⁴⁰ The histologic changes in poliomyelitis are closely similar in primates and man, both with regard to type and distribution of the lesions although we must remember that the development and manifestations of the disease in its initial stages may vary with different portals of entry of the virus.

Discussion of the pathophysiologic features of poliomyelitis must be based primarily on

the histologic lesions which occur in the different stages of the disease although the lesions, both in human and experimental poliomyelitis, show a confusing lack of parallelism with the clinical manifestations in regard to both localization and severity. Clinically, poliomyelitis is primarily a lower motor neuron disease with segmental distribution, yet all observers agree that the histologic lesions are never confined to the spinal cord but are found in a number of other parts of the central nervous system, including the precentral areas of the cerebral cortex. The central motor disturbances are few compared with the rather severe damage found in the motor cortex and in the subcortical centers coordinating motor activity; this is another clear indication of the well known potentiality of different parts of the central nervous system for substitutional activity. Similarly, although severe damage is frequently found in different parts of the medulla oblongata, the occurrence of central respiratory paralysis is, fortunately, rare. On the other hand, the disturbances in emotional behavior which may occur even in non-paralytic cases might be explained by involvement of the hypothalamic centers.⁶¹

In contrast with the older concept of the disease as primarily an interstitial injury the study of experimental poliomyelitis in monkeys has shown beyond doubt that it is the nerve cells which are primarily affected. The virus spreads by way of the axon²³ and it is the large anterior horn cells, especially those in the cervical and lumbar enlargements, which are partic-

* From the Institute of Neurophysiology, University of Copenhagen, Copenhagen, Denmark. Part of this paper was presented at the First International Poliomyelitis Conference, New York, 1948.

ularly susceptible. The inflammatory reaction is secondary. Bodian and Howe⁷ have produced convincing evidence that the presence of living nerve cells is necessary for production of the inflammatory phenomena. When the nerve cells of a center are allowed to degenerate before inoculation with the virus, no inflammatory reaction is produced there although the opposite side, without previous degeneration, shows both nerve cell degeneration and a typical inflammatory response.

Any sign or symptom from the central nervous system might be explained by a diffuse inflammatory reaction, but it seems worth while to attempt a correlation between direct nerve cell injury and the pathophysiologic signs before taking into consideration an accessory influence of edema or other secondary factors.³⁷ Since in many cases a good deal of muscular function is regained in previously paretic muscles in the course of the first months of the disease,³⁷ such a correlation will require the assumption of a possible reversibility of the changes in certain virus-infected parts of the central nervous system. The recovery could, of course, be easily explained by the disappearance of the interstitial mesodermal reaction with its mechanical effects, and it will be difficult to exclude this reaction as a causative agent, but it must be borne in mind that the initial manifestations of the disease usually correspond with specific localizations in the anterior horns. Thus, although nerve cell necrosis and inflammatory infiltration have occasionally been found in the dorsal root ganglia, impairment of sensibility is exceptionable. The absence of sensory changes may, of course, be due to the difficulty in detecting small changes in sensibility by ordinary clinical means and, in fact, studies of the vibratory sensation have in some cases²⁸ but not regularly*

* Dr. M. Iversen has recently examined vibratory sensation in four paralytic cases of poliomyelitis, two during the acute and two during a later stage, without finding significant deviations from normal values for threshold and adaptation.

revealed a lowered threshold indicating a hyperesthetic type of response. The degree of inflammatory reaction as reflected in the spinal fluid has no direct correlation with the progression and reversibility of pareses; furthermore, in poliomyelitis, even in the preparalytic stage, synchronized activity of different motor units of the same muscle has been observed while in cases of meningo-myelitis with evidence of a diffuse inflammatory response this abnormal type of innervation has never been observed except when definite pareses also indicated the presence of anterior horn cell lesions.¹⁸ In my own opinion these observations favor the assumption of a reversible lesion in certain nerve cells. Alternatively, recovery might be interpreted in terms of a substitution of damaged primary internuncial pathways by secondary "delay paths" in the internuncial pool. A comparison of the electrical activity of the spinal cord under the influence of edema and anoxia with that in experimental poliomyelitis might make further differentiation possible. A detailed cytologic analysis by means of more quantitative histochemical methods might also yield useful information with respect to the concepts of reversibility and substitution. An investigation along these lines might even throw light on the important finding that both cooling in water for thirty minutes and exhausting muscular effort during the incubation period of experimental poliomyelitis result in a statistically significant higher incidence of paresis and a more severe degree of motor impairment than is found in controls.⁴¹

The distribution of muscular involvement has given rise to various speculations. In most epidemics the muscles of the lower limb are affected with twice the frequency of those of the upper limb. In the former the quadriceps, anterior tibial and peroneal muscles are mainly affected while in the latter the deltoid, triceps and biceps are affected more frequently than the muscles of the forearm and hand. Recently Hodes³¹ made an interesting attempt to explain this distribution. It is well established that there

is a close relation between velocity of conduction along a nerve fiber and its diameter. He has measured the conduction velocities in nerves to different muscles in both normal and poliomyelitic subjects and has found that the maximal rates of conduction in nerves to paretic muscles are reduced, a finding which is attributed to selective destruction of the motor neurons with fibers of large diameter, the neurons with fibers of small diameter having relatively less affinity for virus. This agrees with the fact that the proximal muscles are more commonly affected than the distal muscles. The largest motor fibers which innervate some of the muscles of the forearm are of greater diameter than the largest fibers innervating the small muscles of the hand. In addition, in earlier experiments it had been shown⁵⁵ that large, heavily myelinated fibers more commonly degenerate than the thinly myelinated or unmyelinated. Further studies of this type might also provide an explanation of the difference in susceptibility of neurons innervating the different proximal muscles of the lower limb.

Recovery after paresis depends both on its severity and on which muscle is affected; the patient's age has not been found to have a significant influence on the degree of recovery.⁶¹ Clinical estimation of the recovery often meets with difficulties due to the scarcely detectable but increasing participation of synergists. Electromyographic examination has shown that recovery in an individual muscle may continue for at least six months. Synchronous activity of different motor units in a muscle, outlasting the third week of the disease, was found to have a less favorable prognosis for the muscle than continuous asynchronous activity in equally paretic muscles. With regard to the recovery of activity in different muscles, the prognosis is considered to be best in the flexor muscles of the fingers, knee and elbow while anti-gravity muscles and the small muscles of the thumb and foot are claimed to have a lower recovery rate.⁶¹ In searching for an

explanation of this difference in the behavior of different muscle groups, differences in the vascularization of different parts of the anterior horns would appear to offer a likely solution. According to Bok,⁹ the cord representation of extensor and abductor muscles in various animals including primates is mainly found along the edges of the anterior horns while the cells supplying flexor and adductor muscles are situated centrally. Temporary anoxia of the lower part of the spinal cord results in cell destruction in the central region of the anterior horns, accompanied by flaccid paresis in the flexor and adductor muscles while the antigravity muscles display a considerable degree of spasticity.³⁸ Since (at least in rabbits) the arteries split up into capillaries mainly at the peripheral parts of the anterior horn, the periphery, representing the extensor muscles, can appropriate more of the available oxygen than the central cells. These observations make it difficult to account for the better recovery of flexor muscles on the basis of circulatory differences at the site of their cord representation.*

Paresis of the urinary bladder, with retention and overflow, and of parts of the gastrointestinal tract belong to the reversible affections in poliomyelitis. Opinions differ widely about the pathophysiology. Fanconi²⁴ considers it an infrequent secondary complication (in 2 per cent of 375 paralytic patients) and interprets it to be due to weakness of the abdominal muscles. Other observers have found urinary bladder paresis in 20 to 65 per cent of paralytic patients; it may occur before the somatic muscles in the extremities are affected. While in the bulbar form of the disease cerebral factors are probably involved in the pathogenesis of urinary bladder paresis, it seems otherwise most likely that the paresis of the urinary bladder, and of the descending colon (causing constipation),

* A discussion of peripheral regenerative phenomena, such as compensatory hypertrophy and outgrowth of axon branches which are important factors in recovery, would be beyond the scope of this paper.

are due to involvement of their parasympathetic innervation. The bladder and descending colon belong to the few viscera having an intramedullary representation of their parasympathetic control derived from small multipolar nerve cells scattered around the base of the ventral horn in the sacral region of the spinal cord. Normally the bladder and the descending colon contract in response to impulses from these cells. The high rate of recovery of these functions may be due either to a temporary lesion of these cells or to an independent automatic activity regulated from peripheral ganglia. The last would be an indication of the large margin of safety which assures the function of autonomic organs.

Stiffness of the muscles of the neck and spine are considered to be signs of a meningeal reaction; they appear early, in the preparalytic stage of the disease. The inflammatory response of the meninges is not very pronounced and its manifestations in the spinal fluid are less marked than in bacterial meningitis. This makes it difficult to interpret the meningeal signs in terms of an inflammatory root involvement. There are other differences between the "meningeal" reaction in poliomyelitis and in true meningitis. McDonald^{52,67} found stiffness of the spine in 80 per cent and stiffness of the neck in 65 per cent of 128 patients with poliomyelitis. In true meningitis stiffness of the neck is usually accompanied by a slight contraction of the hamstring muscles (Kernig's sign), indicating a generalized increase in flexion reflex activity. Although anatomically this is an extensor movement, Fulton²⁹ therefore considers it a part of a flexion reflex to nociceptive stimulation.

In the meningeal phase of poliomyelitis, in contrast with true meningitis, stiffness of the neck is by no means regularly associated with other signs of flexor reflex activity. It was found to be absent in 70 per cent of McDonald's 128 patients. Further, rigidity of the neck and spine muscles is unlike that seen in meningitis; it can be overcome by slight resistance⁶² and it is

striking that the spastic contractions diminish or disappear with the patient in a prone position, a phenomenon which can be produced neither in meningitis nor in the meningism caused by other noxious stimuli such as subarachnoid hemorrhage.¹⁹ Probably this relaxation follows from the inhibition of an exaggerated extensor reflex by slight extension of the flexor muscles of the neck and can be explained in terms of reciprocal innervation.⁴⁷ The stiffness of the muscles of the neck and spine could thus be due to the impairment of central inhibitory mechanisms by early lesions in subcortical centers. The release of both flexor and extensor reflexes is accompanied by repetitive discharges which reach the anterior horn cells. In the case of certain extensor reflexes the "after-discharge" may last for several seconds and is due to continuous discharges in internuncial circuits spread over several segments of the cord.^{26, 43, 44} Inhibitory impulses from vestibular centers and the reticular formation of the medulla oblongata^{50, 51} normally regulate the internuncial activity. Early lesions in these centers could be responsible for exaggerated after-discharges in postural contractions from the muscles of the neck and spine.

In experimental poliomyelitis spasticity can be present at an early stage at which neither virus nor histologic lesions are detectable in corresponding parts of the spinal cord while pathologic changes in the brain, especially in the reticular formation, are fully developed.⁶

The occurrence of "spasm" in paralytic and non-paralytic muscles has been the subject of intensive discussions and controversies. It is well known that in early poliomyelitis both hyperactivity of the stretch reflexes and clonus occur but are soon followed by their diminution or disappearance. The occurrence of muscle spasms in both paretic and unaffected muscles of the limbs during and after the acute phase of the disease is thought to contribute considerably to disability.^{59, 60} The conception of spasm in poliomyelitis has not always

been clearly defined, but most investigators consider it to be the result of increased myotatic reflex activity. This increase which, as already mentioned, does not exhibit itself by high, deep reflexes, is thus of an entirely different type from that which characterizes, for example, the response of the muscles of a spastic spinal paresis to slight passive movements. Recordings of action potentials have shown that passive stretch is associated with discharges of longer duration than in the normal.¹¹ However, this effect—interesting enough when present—is very variable from epidemic to epidemic and sometimes many large groups in an epidemic are free from spasm even when tested with action currents. This agrees with our observations in forty-seven patients in 1942¹⁸ and more recently in twenty-seven patients during the 1947 epidemic.¹⁹ In these cases there was neither activity at rest nor did passive movements show reactions in any way deviating from those of normal muscle. Thus there is a definite difference from the true spastic activity which almost regularly occurs in the muscles of the neck and the spine. However, the sustained activity observed by several investigators is a very interesting phenomenon, provided it occurs with passive movements too small to pass the threshold of pain which may be rather low in these muscles.

The pathophysiologic explanation of this spastic activity is still open to discussion. It has been explained¹¹ by assuming a replacement of the single neuron reflex arc, normally responsible for myotatic activity, by multineuron arcs, possibly associated with the disappearance of inhibitory impulses. In this connection it is interesting to recall that the histologic changes are never confined to the anterior horn cells alone but are seen also in the internuncial cell groups at the same levels. Kabat and Knapp's³⁵ suggestion, that lesions of the internuncial cells in regions of the cord where the anterior horn cells proper are hardly affected might explain spastic reactions, has been refuted by other investigators.^{6,22}

Muscle pain is felt especially when the muscle is contracted. It occurs early in the disease, mainly in the muscles of the lower limb and often in those muscle groups which later become paretic. Apparently it is of purely peripheral origin and there is no evidence of root involvement. Although it may be compared with sensations after vigorous exercise, it is hardly caused by latent "spastic" activity. It is not relieved by curarine.^{27,54} The origin of pain and tenderness in poliomyelitis is still obscure as it is in a number of other infectious diseases (e.g., influenza) and in the majority of cases of local palpable muscle affections. Only in less than 20 per cent* of forty-six patients suffering from these affections did resting muscles show a constant activity which did not disappear with adequate relaxation, diverting the attention or a change of position.¹⁴ However, in the majority of painful affections the electromyogram does not differ from that of normal muscle. It is possible that the changes in the capillary blood circulation, which Knisely³⁶ has observed in experimental poliomyelitis and in a number of other pathologic conditions, give rise to foci of anoxia in muscle and that the abnormal metabolites produced in these foci stimulate the pain endings which are especially numerous near the blood vessels and the tendinous insertions of a muscle; the latter position is in agreement with the localization of muscle pain to the insertions. Other factors causing stimulation of the pain endings cannot, however, be excluded and a more extensive use of muscle biopsy may yield information on this problem.

Ordinary methods of electromyographic examination have also proved useful in the assessment of paresis and of the stage of denervation in poliomyelitis when applied to studies of voluntary and electrically induced activity.^{2,15,32,58} They make it possible to determine whether the paralysis is complete or not and provide a delicate means of assessing the condition of the

* This figure refers to chronic, therapy-resistant patients with intermuscular fibrositis.

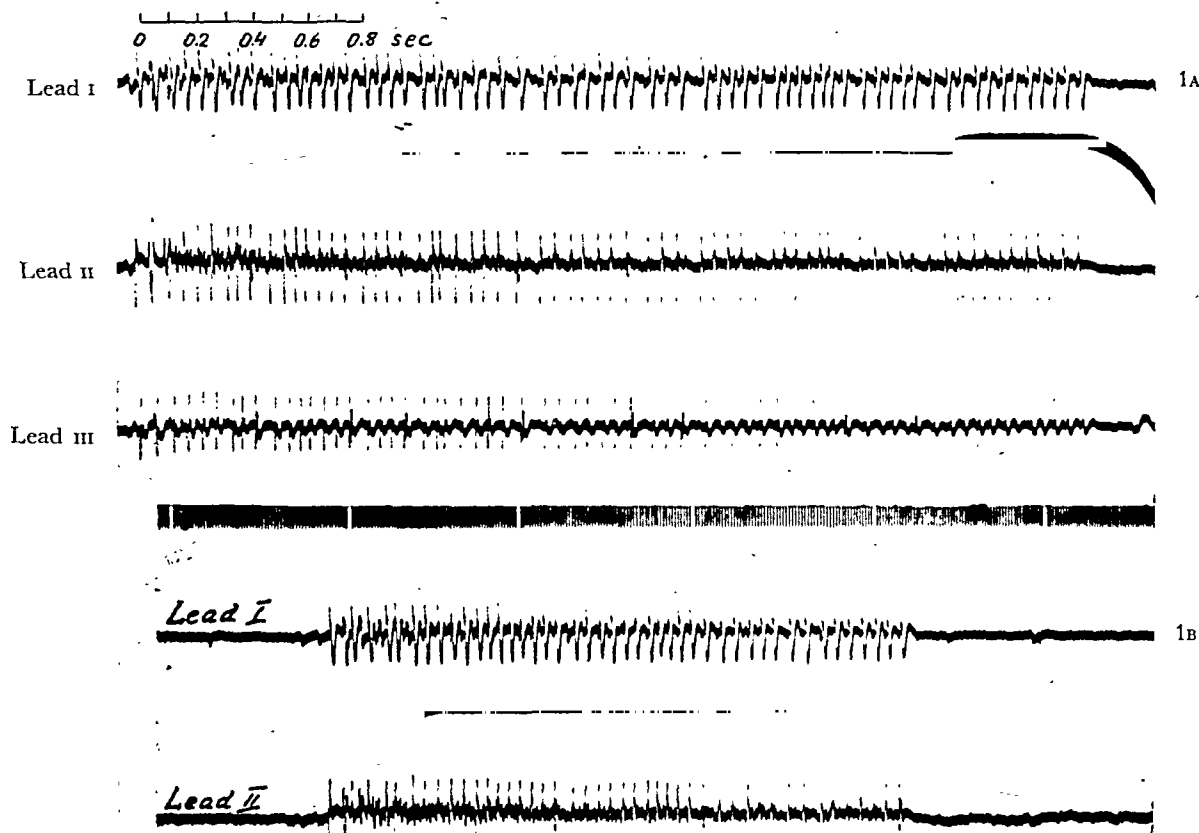


FIG. 1. Action potentials and mechanical response of paretic biceps muscle (previous poliomyelitis).¹⁴ A, lead I: concentric needle electrode, frequency 17.3/second. Lead II: two needle electrodes 15 mm. apart at a distance of 2 cm. from lead I, frequency 17.3/second. Lead III: concentric needle electrode at a distance of 2 cm. from lead II, frequency 17.3/second. B, as A, frequency in all three leads 18.6/sec. Distance between time marks 10 milliseconds.

motor nerve and corresponding nerve cells. They can give an expression of the number of active nerve cells and detect minor degrees of lower motor neuron damage.

When the number of active motor units is reduced, as is the case in poliomyelitis and in partial lesions of the peripheral nerves, individual spike potentials can be recorded during maximal effort without interference from the activity of neighboring fibers. In genuine muscular atrophy maximum contraction is generally accompanied by the interfering electrical activity of many motor units since even slight contractions demand a wider spread of innervation than in normal muscle; it is therefore more difficult to record single discharges in these cases than in normal muscles or in muscles with neurogenic paresis.

In slight paresis the electromyogram may show a transitory state in which, although such interfering activity is found, the activity of the neighboring units is so reduced that the fiber situated nearest to the electrode dominates the curve.¹⁵ Isolated action potentials, together with the presence of "silent areas," are found in severe paresis and correspond to the histologic picture of the loss of numerous motor units where only scattered islands of normal tissue are seen on a background of degenerated muscle tissue. In mild atrophy large and small patches of degenerated tissue occur in the midst of normal tissue and correspond to a lesser decrease in the number of active motor nerve cells and of muscle fibers controlled by them. The histologic picture of sharply demarcated patches of atrophy is typical

of these lesions in contrast to the more diffuse distribution of changes in purely myogenic atrophy. By electromyography it is also possible to distinguish between degenerative lesions of the lower motor neuron and affections in which there is temporary impairment of conduction in the axon. In denervation, fibrillation gives rise to a characteristic action potential of extremely short duration (one to two milliseconds).⁶⁵ It is presumably this type of potential which has been recorded several weeks after the initial stage in poliomyelitis as in other forms of denervation.^{58,63} The reappearance of motor unit potentials of normal duration (five to ten milliseconds) can be considered an early sign of recovery. The origin of the fibrillation is still obscure; it is scarcely affected by curarine and cannot be explained by assuming increased formation or delayed destruction of acetylcholine.⁵³

By leading off simultaneously from different regions of the same muscle, i.e., from different motor units the atrophy can be further differentiated since synchronous activity has been observed when the anterior horn cells are affected. This synchronization occurs during both weak and strong contractions. (Fig. 1.)^{15,16} In non-fatigued normal muscle and in muscle with neurogenic atrophy caused by diseases of the nerve roots or of the peripheral nerves, synchronous activity may occur as a transient phenomenon but it did not continue after the appearance of variation in frequency with variations in contraction intensity. In amyotrophic lateral sclerosis and spinal muscular atrophy it has been found in muscles before they showed any other signs of involvement. In poliomyelitis, as already mentioned, it can appear as early as one day before the onset of paresis. (Fig. 2.) This points to a connection with partial damage to some nerve cells. Neither a compensatory mechanism to mobilize simultaneously the largest possible number of remaining motor units in a given muscle, nor a manifestation of disturbances in reciprocal innervation characterized by

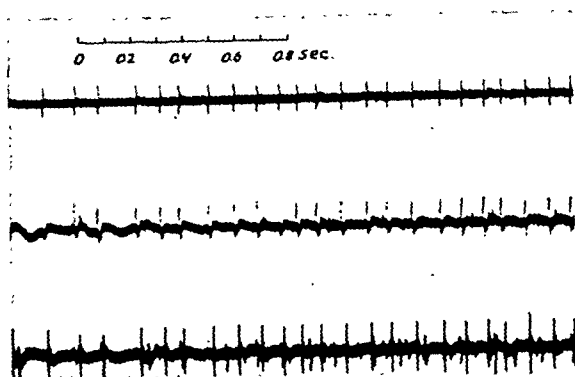


FIG. 2. Synchronous activity in a paretic vastus medialis in the initial phase of poliomyelitis.¹⁷ Three concentric needle electrodes inserted to different depths 2 cm. apart. Distance between time marks 10 milliseconds.

simultaneous activity in agonists and antagonists of the same movement seems a likely explanation. On the other hand, synchronous single impulses also may rarely occur in two different muscles, although only in the most severely paretic stage and in contrast with the disturbances of reciprocal innervation to be mentioned this effect is irreversible.⁶⁴ It appears to the author that the same interpretation would apply here as he suggested to follow for the occurrence of synchronization in the same muscle. When testing for synchronization of potentials in the same muscle, technical artefacts have to be eliminated,* but a discussion of these problems would go beyond the scope of this paper. In extreme degrees of neurogenic atrophy, of whatever origin, there is an increased chance of picking up potentials from the same motor unit with different electrodes; this possibility must always be excluded when "true" synchronization of different motor units is used for differential diagnosis. However, when cautiously evaluated, its occurrence is a useful aid to diagnosis. For instance, in seven patients with polyradiculitis, some of them examined in the acute stage, no synchronous activity could be found despite severe

* This can be achieved by procedures which are familiar from similar electrophysiologic problems, i.e., mainly by using differential amplification and by leading off with symmetrical electrodes using a platinum cannula with two thin isolated platinum wires at a very short distance. Obviously a more primitive technique demands special precautions and experience in avoiding artefacts.

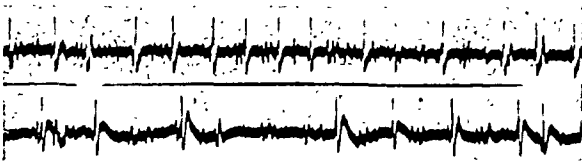


FIG. 3. Increasing fatigue in tibialis anterior with neurogenic atrophy of peripheral origin. The lower record is a direct continuation of the upper. Concentric needle electrode.

paralysis and reduction in the number of motor units.

The cause of synchronization must still be discussed on a somewhat hypothetical basis. It has been observed in decerebrate cats during myotatic activity.⁵ However, in cases of anterior horn cell damage there did not seem to be any positive correlation between the occurrence of synchronization and the presence of exaggerated stretch reflex activity; on the contrary, in most cases there was evidence of diminished myotatic response. In the physiology of the nervous system synchronization of excitation processes has been considered to be due to the interaction of neighboring cells discharging rhythmically.^{1,12,25,56} Partial injury of a nerve cell could facilitate an irradiation of impulses without otherwise disturbing its function and this assumption agrees with the observation that in a muscle with synchronized activity, as in poliomyelitis, the start of volitional contraction is frequently accompanied by muscle action potentials of relatively high frequency. Both normal and neurogenically atrophic muscle without synchronous innervation can begin a contraction with relatively low frequency. The high initial frequency in a muscle showing synchronization could be caused by mutual spreading of excitation (spatial summation) reaching the nerve cells with a minor and decreasing phase difference. Another explanation would be a retained activity of nerve cells with high synaptic concentrations and common internuncial pathways, and this would be compatible with the observation that mainly the spike potentials of higher amplitude are found to synchronize.

Attempts recently have been made in this

laboratory to obtain a quantitative expression of synchronization of different motor units using electronic counting devices which directly give the percentage coincidence of impulses from different regions of the same muscle.²⁰ These investigations, although still at a preliminary stage, have given promising results. In normal muscle at a given frequency range the degree of coincidence is only slightly greater than that which can be expected statistically (3 to 4 per cent). During fatigue coincidence increases considerably (20 to 35 per cent) but it never reaches the level which is found in nearly all cases of affections of the anterior horn cells (80 to 90 per cent).

Simultaneous discharges to both agonist and antagonist is a most important disturbance of normal reciprocal innervation which has been observed in poliomyelitis.^{10,11,63,64} It belongs to an abnormality which can be overcome by re-education and may be compared with the initial behavior of a flexor muscle (e.g., biceps femoris) after transposition to the extensor side.⁶⁶ In the first stage the transplant still receives impulses in the flexor phase of a movement. However, after only a few trials, in which visualization of the task seems to be more important than actual visual control and proprioceptive hints, it can also contract in an extensor phase. For some time it contracts in both phases and there is no evidence of automatic recovery of normal reciprocal innervation; then, after a certain period of practice the transplanted flexor is inactive during contractions of the other flexors. However, even years after transplantation, relapses to its native function may occur and are considered to be evidence that re-education does not replace the elementary motor mechanisms for flexor activity but rather that the substituted action develops at higher coordinating levels and can effectively outdo but not abolish natural coordination.

A similar mechanism could explain the re-coordination of certain movements in poliomyelitis when part of a synergy remains permanently paralyzed. At present,

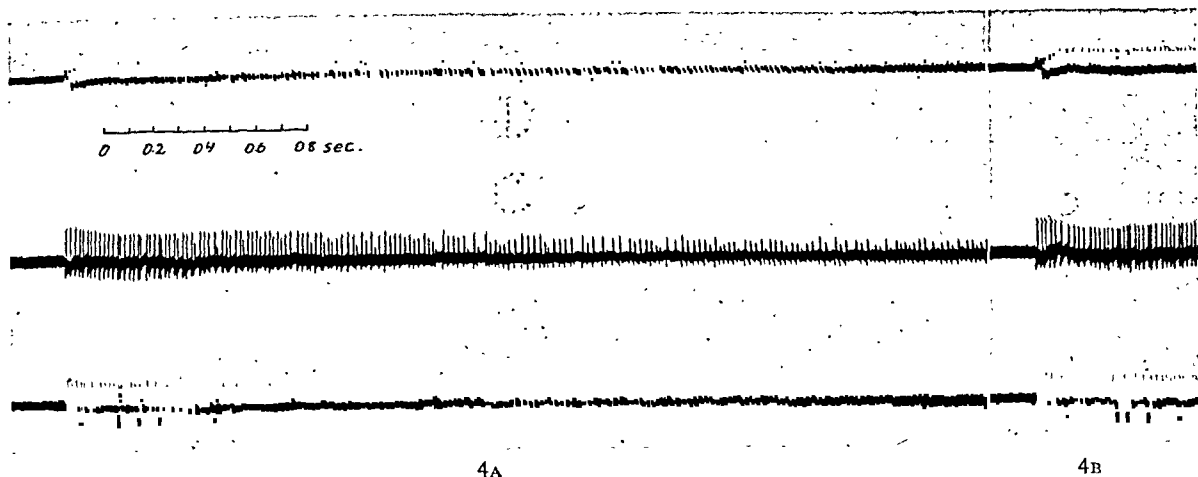


FIG. 4. Paresis after previous poliomyelitis,¹⁷ three concentric needle electrodes in vastus medialis. A, fatigue with gradual decrease in the amplitude of action potentials; B, after about 1 minute rest.

however, it is difficult to decide at what level of the cord to look for the primary disturbances of reciprocal innervation. Evidence has recently been brought forward that internuncial activity is not necessarily involved in the inhibition of the antagonist which characterizes reciprocal innervation.^{45,46} Interference from the internuncial pool with monosynaptic motor activity might possibly account for disturbances in reciprocal innervation. In animal experiments a definite correlation has been demonstrated between the different phases of the slow cord potentials and the periodically alternating discharges in flexor and extensor muscles. The direction of these potentials is at the same time associated with facilitation (root positivity) or inhibition (root negativity) of flexor reflex activity.⁴ Phenomena of periodic facilitation and inhibition might result from these slow cord potentials and knowledge about their behavior in the poliomyelitic animal might contribute toward elucidation of the mechanism responsible for the disturbances in reciprocal innervation.

So far the evidence of a peripheral element in the impairment of motor function has not been discussed. However, unquestionable signs of peripheral motor alterations, apart from atrophy, do exist. Fatigue in both normal and paretic muscle, independent of the cause of the paresis, manifests itself as a reduction in the number of

action potentials and not as a significant decrease in the amplitude of the individual spike. (Fig. 3.) This applies to poliomyelitis in the first four to six weeks, but in its later stages an entirely different effect of fatigue is seen, i.e., the amplitude of the



FIG. 5. Fatigue during maximal effort³ action potentials led off from vastus medialis with concentric needle electrode (previous poliomyelitis). A, after 1 second, temperature 36.1°C. B, after 19 seconds, temperature 36.1°C. C, after 34 seconds, temperature 36.6°C. Distance between time marks 20 milliseconds.

individual spike decreases gradually with fatigue. (Fig. 4.)¹⁸ These observations have been confirmed lately [by Hodes³³; the decrease in amplitude also occurs in the course of repetitive electrically-induced contractions. Prostigmine partially counteracts the abnormal electrical response. The effect is comparable with the gradual decrease in amplitude of action potentials in partial curarization or in myasthenia gravis,³¹ and it therefore seems probable that it is connected with changes at the neuromuscu-

lar junction. According to Hodes³³ this effect should be due to the dropping out of some muscle fibers or whole motor units, i.e., a mechanism which also occurs in fatigue of normal muscle. When the leading off is done with surface electrodes, which

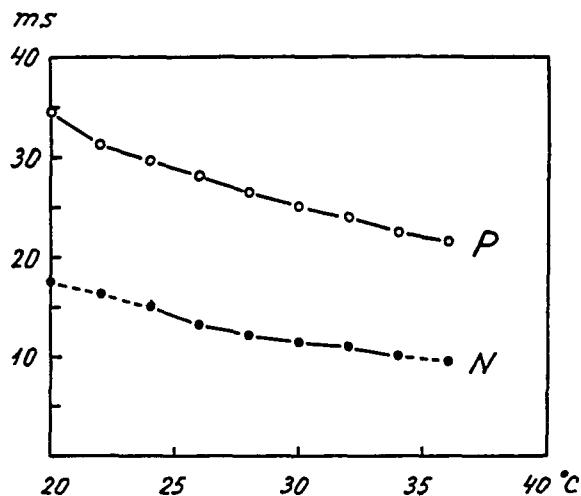


FIG. 6. Duration of action potential (ms) as function of intramuscular temperature in normal (n) and previously poliomyelitic (p) muscle.

integrate over a large number of active units, it is difficult to decide whether this is the only reason. On the other hand, the individual diphasic action potential, as it is led off with a concentric needle electrode, shows the same *gradual* decrease in amplitude without any significant change in duration. (Fig. 5.)^{13,18} Thus, an exception to the all-or-none rule which otherwise determines the amplitude of action potentials in normal muscle fibers is suggested.

We have looked for further abnormalities in neuromuscular transmission. Compared with normal muscle, *denervated muscle* in most animals and in man has an increased sensitivity to intra-arterially applied acetylcholine.¹⁷ Examinations of isolated muscle fibers reveal that even in denervated muscle this effect is due to a lowering of the threshold of a region in the fiber of high acetylcholine sensitivity which corresponds histologically with the nerve ending.³⁹ In poliomyelitis, even with a severe degree of paresis (i.e., denervation), neither the motor nor the vasomotor response to intra-arterial acetylcholine corresponds with those

seen in denervation from other causes. Our preliminary results seem to indicate that the lowering of threshold is less marked than in, e.g., amyotrophic lateral sclerosis or peripheral denervation.

So far we have not been able to apply

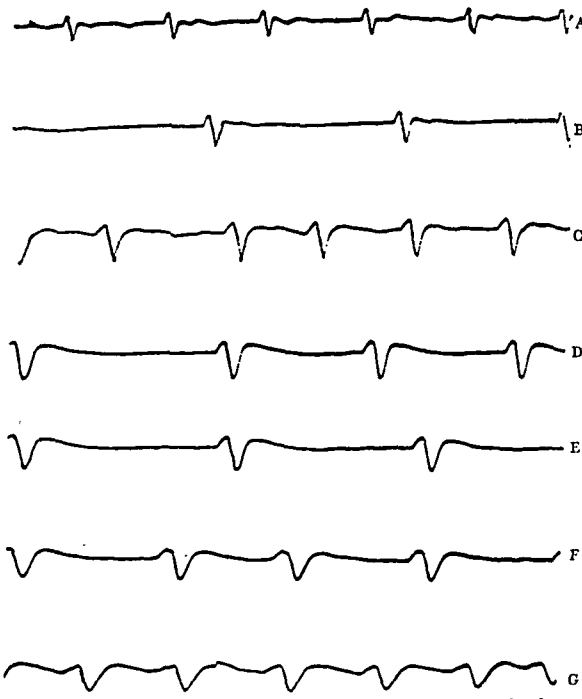


FIG. 7. Action potentials at decreasing intramuscular temperature in previously poliomyelitic muscle³ led off with concentric needle electrode. A, 36.1°C.; B, 33.7°C.; C, 26.3°C.; D, 20.6°C.; E, 18.7°C.; F, 17.7°C.; G, 17.7°C. Distance between time marks 20 milliseconds.

these tests, except for the effect of fatigue, in the early stage of the disease; this applies also to comparisons of the duration, amplitude and shape of the individual spike potential with those found in normal muscle and in neurogenic atrophy of peripheral origin. However, the results obtained from observations in later stages of the disease may be worth mentioning in this connection.

In normal muscle the first phase (spike) of the diphasic action potential was found to last 4.6 milliseconds.* In poliomyelitis as in other cases of neurogenic atrophy the duration is considerably increased and values of 11.5 to 12.5 milliseconds were measured for the spike duration.¹⁵ This

* Standard deviation 7.4 per cent, 245 measurements on sixteen different persons.

difference might be due to the 2 to 5°C. lower values of intramuscular temperature which are frequently present in poliomyelitis. But later investigations³ have demonstrated that the temperature effect on the action potentials is identical in normal and poliomyelitic muscle (Fig. 6); in both, a decrease of 10°C. in the temperature range investigated results in an increase in the spike duration of 35 per cent, the action potential of poliomyelitic muscle having double the duration of that of normal muscle even when the two are compared at the same intramuscular temperature. In poliomyelitis the lower intramuscular temperature will cause a lower propagation velocity of the wave of excitation over the fiber and this difference may account for the difficulties encountered in the activation of poliomyelitic muscles at a low temperature. (Fig. 7.)

The amplitude of the action potential has a maximum at 25 to 30°C. in both normal and poliomyelitic muscles and in both, anoxia, investigated at a constant intramuscular temperature, causes a decrease in amplitude after 30 to 40 minutes. (Fig. 8.) In poliomyelitic muscle this decrease in amplitude is also accompanied by a decrease in duration of approximately 20 per cent. When fatigue is combined with either anoxia or low temperature, the two effects on the action potential are superimposed.

The abnormalities found in the electrical response thus clearly indicate that peripheral structures are involved in the pathologic physiology of the sequelae after poliomyelitis. Whether this involvement is the result of a direct action of the virus on the neuromuscular junction or is due to a secondary reaction following degenerative processes of a specific nature in the central nervous system remains an open question. For the time being the assumption of a secondary involvement appears more probable. An investigation of the effect of repetitive electrical stimulation in the acute stage might help to answer this question. Abnormalities, which at this

stage of the disease are not yet apparent in voluntary contraction, might thereby be revealed.

It is my impression that the study of the pathologic physiology of autonomic disturbances in both the early and later

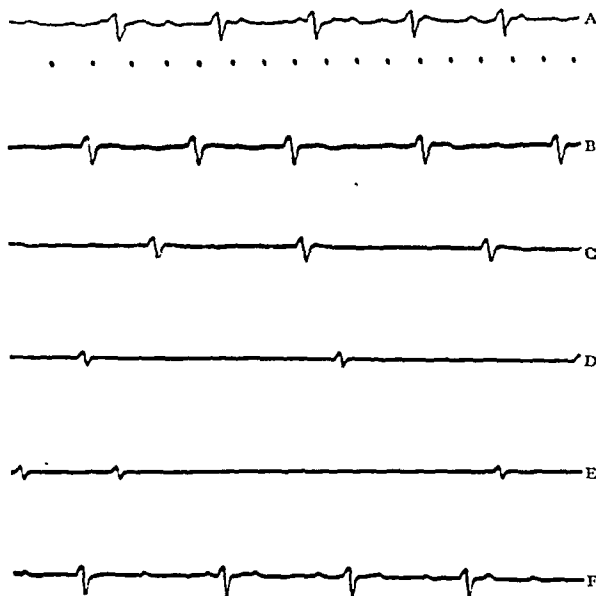


FIG. 8. Action potentials during anoxia³ led off with concentric needle electrode, intramuscular temperature kept constant at 38.3 to 38.5°C. (previous poliomyelitis). A, 0 minutes; B, 37 minutes; C, 40 minutes; D, 44 minutes; E, 44.5 minutes; F, after eight-minute restitution. Distance between time marks 20 milliseconds.

stages of poliomyelitis has been rather neglected. Urinary bladder paresis which occurs in the acute phase has been previously discussed. In addition, abnormal reactions of skin temperature to indirect heating have also been described in severe cases in which bulbar involvement probably existed.⁴⁸ Normally, immersion of the lower extremities in water at a temperature of 42 to 44°C. causes a rise in the skin temperature of previously cooled fingers of about 10°C. The rise is abrupt and occurs after a latent period of 1.5 to 21.5 minutes, the rate of the rise being 3 degrees/minute.^{21,30,42} Temperature changes in the skin are considered to be due to changes in the peripheral blood supply caused by changes in central vasomotor regulation, the tone of the vasomotor center reacting to small changes in blood temperature. In

a few cases of severe poliomyelitis the skin temperature of the fingers did not respond to indirect heating in the early phase of the disease but a normal response was observed later. Although it is not surprising to find disturbances in central vasomotor regulation in the early stage of poliomyelitis, these findings should be controlled by similar tests in patients with corresponding febrile signs and symptoms due to other causes before they can be accepted as conclusive evidence for a specific effect of poliomyelitis on autonomic activity. In the later stages of the disease and in slight cases without clinical signs of bulbar involvement no abnormal response in skin temperature could be recorded. Thus it remains an open question whether the signs of circulatory disturbances which are present, especially in the later stages of poliomyelitis, are secondary to the inactivity or are due to direct damage to the autonomic ganglia. The inactivity could also account for the low intramuscular temperature found in the paretic muscles. Although views with regard to the histologic evidence for damage to these ganglia are still somewhat conflicting, in monkeys the peripheral ganglia are definitely not specifically affected.⁸ In man, damage was found in certain ganglia but the sympathetic chain usually escaped.²² In patients with cervical cases the sympathetic centers in the lateral horns were found to be only rarely involved.⁶⁷ These observations are in agreement with the assumption that it is principally neurons with fibers of large diameter which are susceptible to virus.^{34,55}

REFERENCES

1. ARVITANAKI, A. Interactions électriques entre deux cellules nerveuses contriquées. *Arch. internat. de physiol.*, 52: 381, 1942.
2. BAUWENS, P. Electro-diagnosis and electrotherapy in peripheral nerve lesions. *Proc. Roy. Soc. Med.*, 34: 459, 1941.
3. BENTSEN, K. G. Single potentials from human muscles during fatigue, anoxia and temperature variations; *Nord. med.*, 25: 697, 1945.
4. BERNHARD, C. G. and THERMAN, P. O. On the mechanism of reciprocal innervation. *Acta physiol. Scandinav.*, 13: 162, 1947.
5. BERNHARD, C. G. and THERMAN, P. O. Rhythmical activity of motor units in myotatic reflexes. *Acta physiol. Scandinav.*, 14: 47: 4, 1947.
6. BODIAN, D. Experimental evidence on the cerebral origin of muscle spasticity in acute poliomyelitis. *Proc. Soc. Exper. Biol. & Med.*, 61: 170, 1946.
7. BODIAN, D. and HOWE, H. A. Experimental studies on intraneural spread of poliomyelitis virus. *Bull. Johns Hopkins Hosp.*, 68: 58, 1941.
8. BODIAN, D. and HOWE, H. A. The significance of lesions in peripheral ganglia in chimpanzee and in human poliomyelitis. *J. Exper. Med.*, 85: 231, 1947.
9. BOK, S. T. B. Das Rückenmark. Handbuch der mikroskopischen Anatomie des Menschen. Vol. 4, p. 478. Berlin, 1928. Julius Springer.
10. BOUMAN, H. D. and SCHWARTZ, R. P. Degree, extent and mechanism of muscle spasm in infantile paralysis. *New York State J. Med.*, 44: 147, 1944.
11. BOUMAN, H. D. Some physiological aspects of infantile paralysis. *Physiotherapy Rev.*, 27: 221, 1947.
12. BREMER, F. L'activité électrique "spontanée" de la moelle épinière. *Arch. internat. de physiol.*, 51: 211, 1941.
13. BROWN, G. L. The action of acetylcholine on denervated mammalian and frog's muscle. *J. Physiol.*, 89: 438, 1937.
14. BUCHTHAL, F. and CLEMMESSEN, Sv. On the differentiation of palpable muscle affections by electromyography. *Acta med. Scandinav.*, 105: 48, 1940.
15. BUCHTHAL, F. and CLEMMESSEN, Sv. On the differentiation of muscle atrophy by electromyography. *Acta psychiat. et neurol.*, 16: 143, 1941.
16. BUCHTHAL, F. and CLEMMESSEN, Sv. The electromyogram of atrophic muscles in cases of intramedullary affections. *Acta psychiat. et neurol.*, 18: 377, 1943.
17. BUCHTHAL, F. and ENGBÆK, L. On the neuromuscular transmission in normal and myasthenic subjects. *Acta psychiat. et neurol.*, 23: 1, 1948.
18. BUCHTHAL, F. and HØNCKE, P. Electromyographical examination of patients suffering from poliomyelitis ant. ac. up to 6 months after the acute stage of the disease. *Acta med. Scandinav.*, 116: 148, 1944.
19. BUCHTHAL, F. and LASSEN, H. C. Unpublished, 1948.
20. BUCHTHAL, F. and MADSEN, A. Unpublished experiments.
21. CHRISTIANSEN, Sv., FOG, M. and VANGGAARD, T. The cerebral vasomotor regulation. A method for determination of the cerebral control of peripheral circulation in man. *Acta psychiat. et neurol.*, 14: 413, 1939.
22. FABER, H. K. and SILVERBERG, R. J. A neuropathological study of acute human poliomyelitis with special reference to the initial lesion and to various potential portals of entry. *J. Exper. Med.*, 83: 329, 1946.
23. FAIRBROTHER, R. W. and HURST, E. W. Pathogenesis of, and propagation of virus in experimental poliomyelitis. *J. Path. & Bact.*, 33: 17, 1930.
24. FANCONI, G. Die Poliomyelitis und ihre Grenzgebiete. Basel, 1944.

25. FESSARD, A. Hypothèse sur le mécanisme d'intervention du facteur électrique dans la synchronisation interneuronique. *Compt. rend. Soc. de biol.*, 136: 268, 1942.
26. FORBES, A. The interpretation of spinal reflexes in terms of present knowledge of nerve conduction. *Physiol. Rev.*, 2: 361, 1922.
27. FOX, M. J. Curare in the treatment of acute poliomyelitis. *J. A. M. A.*, 131: 278, 1946.
28. FROHRING, W. O., KOHN, P. M., BOSMA, J. F. and TOOMEY, J. A. Changes in the vibratory sense of patients with poliomyelitis as measured by the Pallesthesiometer. *Am. J. Dis. Child.*, 69: 89, 1945.
29. FULTON, J. F. *Physiology of the Nervous System*. London, 1943. Oxford University Press.
30. GIBBON, J. H. and LANDIS, E. M. Vasodilation in the lower extremities in response to immersing the forearms in warm water. *J. Clin. Investigation*, 11: 1019, 1932.
31. HARVEY, A. M. and MASLAND, R. L. The electromyogram in myasthenia gravis. *Bull. Johns Hopkins Hosp.*, 69: 1, 1941.
32. HARVEY, A. M. and KUFFLER, S. W. Motor nerve function with lesions of the peripheral nerves. *Arch. Neurol. & Psychiat.*, 52: 317, 1944.
33. HODES, R. An electromyographic study of defects of neuromuscular transmission in poliomyelitis. *Arch. Neurol. & Psychiat.*, 59: 436, 1948.
34. HODES, R. Personal communication, 1948.
35. KABAT, H. and KNAPP, M. E. The mechanism of muscle spasm in poliomyelitis. *J. Pediat.*, 24: 123, 1944.
36. KNISELY, M. Personal communication.
37. KRISTENSEN, G. S. and WULFF, F. On the course of paralysis in poliomyelitis patients. *Acta med. Scandinav.*, 127: 361, 1947.
38. KROGH, E. Effect of acute anoxia on the large motor cells in the spinal cord. *Acta physiol. Scandinav.*, 10: 271, 1945.
39. KUFFLER, S. W. Specific excitability of the endplate region in normal and denervated muscle. *J. Neurophysiol.*, 6: 99, 1943.
40. LANDSTEINER, K. and POPPER, E. Mikroskopische Präparate von einem menschlichen und zwei Affenrückenmarken. *Wien. klin. Wchnschr.*, 21: 1830, 1908.
41. LEWINSEN, S. O., MILZER, and LEWIN, P. Effect of fatigue, chilling and mechanical trauma on resistance to experimental poliomyelitis. *Am. J. Hyg.*, 42: 204, 1945.
42. LEWIS, T. and PICKERING, G. W. Vasodilation in the limbs in response to warming the body; with evidence for sympathetic vasodilator nerves in man. *Heart*, 16: 33, 1932.
43. LLOYD, D. P. C. The spinal mechanism of the pyramidal system in cats. *J. Neurophysiol.*, 4: 525, 1941.
44. LLOYD, D. P. C. Reflex action in relation to pattern and peripheral source of afferent stimulation. *J. Neurophysiol.*, 6: 111, 1943.
45. LLOYD, D. P. C. Facilitation and inhibition of spinal motoneurons. *J. Neurophysiol.*, 9: 421, 1946.
46. LLOYD, D. P. C. Integrative pattern of excitation and inhibition in two-neuron reflex arcs. *J. Neurophysiol.*, 9: 439, 1946.
47. LIDELL, E. G. T. and SHERRINGTON, C. S. Reflexes in response to stretch (myotatic reflexes). *Proc. Roy. Soc., London*. 96B: 212, 1924.
48. LUNDBÆK, K. Experimental investigations on the function of the autonomic nervous system during the acute phase of poliomyelitis. *Acta med. Scandinav.*, 114: 565, 1943.
49. LUNDVOLD, A. Can synchronous units seen on electromyography be an artificial product? *Acta psychiat. et neurol.*, 22: 249, 1947.
50. MAGOUN, H. W. Bulbar inhibition and facilitation of motor activity. *Science*, 100: 549, 1944.
51. McCULLOCH, W. S., GRAF, C. and MAGOUN, H. W. A cortico-bulboreticular pathway from area 4-s. *J. Neurophysiol.*, 9: 127, 1946.
52. McDONALD, S. F. Signs and symptoms of the acute stage of anterior poliomyelitis in the 1931-1932 epidemic. *M. J. Australia*, 1: 1, 1933.
53. MEAD, S. Some properties of denervated muscle. *Arch. Physical Med.*, 28: 93, 1947.
54. NORMANN, N. Kurare i behandlingen av poliomyelitt. *Nord. med.*, 37: 476, 1948.
55. O'LEARY, I. L., HEINBECKER, P. and BISHOP, G. H. Nerve degeneration in poliomyelitis, physiologic and histologic studies on the root and nerves supplying paralyzed extremities of monkeys during acute poliomyelitis. *Arch. Neurol. & Psychiat.*, 28: 272, 1932.
56. RENSHAW, B. and THERMAN, P. O. Excitation of intraspinal mammalian axons by nerve impulses in adjacent axons. *Am. J. Physiol.*, 133: 96, 1941.
57. SCHEINKER, M. Histopathologic findings in human poliomyelitis. *Tr. Am. Neurol. A.*, 33, 1946.
58. SCHWAB, R. S., WATKINS, A. L. and BRAZIER, M. A. B. Quantitation of muscular function in cases of poliomyelitis and other motor nerve lesions. *Arch. Neurol. & Psychiat.*, 50: 538, 1943.
59. SCHWARTZ, R. P. and BOUMAN, H. D. Muscle spasm in the acute stage of infantile paralysis as indicated by recorded action current potentials. *J. A. M. A.*, 119: 923, 1942.
60. SCHWARTZ, R. P., BOUMAN, H. D. and SMITH, W. K. The significance of muscle spasm. *J. A. M. A.*, 126: 695, 1944.
61. SKINHØJ, E. Nogle Poliomyelitisproblemer. Submitted as a thesis to the University of Copenhagen, 1948.
62. TOOMEY, J. A. Diagnosis of poliomyelitis. *J. A. M. A.*, 117: 269, 1941.
63. WATKINS, A. L., BRAZIER, M. A. B. and SCHWAB, R. S. Concepts of muscle dysfunction in poliomyelitis. *J. A. M. A.*, 123: 188, 1943.
64. WATKINS, A. L. and BRAZIER, M. A. B. Studies on muscle innervation in poliomyelitis and nerve injuries. *Arch. Physical Med.*, 26: 69, 1945.
65. WEDELL, G., FEINSTEIN, B. and PATTLE, R. E. Electrical activity of voluntary muscle in man under normal and pathological conditions. *Brain*, 67: 178, 1944.
66. WEISS, P. and BROWN, P. F. Electromyographic studies on recoordination of leg movements in poliomyelitis patients with transposed tendons. *Proc. Soc. Exper. Biol. & Med.*, 48: 284, 1941.
67. WILSON, S. A. K. *Neurology* 1. London, 1940. Arnold Co.

Clinical Aspects of Acute Poliomyelitis*

DOROTHY M. HORSTMANN, M.D.

New Haven, Connecticut

THE older habit of classifying clinical forms of poliomyelitis according to elaborate schemes based on clinical evidence of the site of central nervous system involvement has fallen into disuse, and today a simpler, more workable classification is preferred. One which is in common usage and will be adopted in this paper designates *abortive*, *non-paralytic* and *paralytic* types, and fits various cases including spinal, bulbar and encephalitic into this framework. The *abortive* form is defined as a symptomatically non-specific, mild, brief illness without clinical evidence of CNS involvement; the *non-paralytic* as one in which clinical signs of CNS disturbance appear but nerve cell damage is not severe enough to produce weakness or paralysis; and the *paralytic* type in which definite muscle weakness or paralysis develops.

Since poliomyelitis is a common acute infection which only occasionally is associated with clinical evidence of CNS involvement, the abortive form of the disease is far more common than are the non-paralytic and paralytic types. Paul and Trask,¹ on the basis of house to house surveys carried out in 1931 and 1932, estimated the ratio of abortive to frank cases (non-paralytic and paralytic) to be about 9:1. Recently, however, evidence has appeared which makes it probable that the number of abortive cases has been underestimated, and they may outnumber the others by 20 to 1 as determined by Sweetnam in England,² or even several hundred to 1 as estimated in a recent epidemic in New Zealand.³ The amount of virus calculated to be present in urban sewage from a large city when only a few definite cases were

apparent⁴ supports the latter figure, since it is likely that sewage virus is derived from unrecognized mild abortive cases as well as from asymptomatic carriers. In any event the cases in which paralysis occurs represents a small fraction of the total infections.

Abortive Poliomyelitis. Many, probably most, patients with abortive poliomyelitis are never seen by a physician and are not included in statistics of reported cases because no specific clinical diagnosis can be made. However, in spite of the fact that it is so non-specific an illness clinically, it seems likely that abortive poliomyelitis is sometimes, if not often, correlated with actual invasion of the central nervous system by the infective agent. An earlier concept that this brief febrile episode—sometimes termed a “minor illness”⁵—represents a systemic reaction to a generalized infection, preceding the central nervous system invasion or passage of the blood-brain barrier⁶ is no longer tenable. At least in the experimental disease, as shown by Bodian and Howe,⁷ scattered but at times extensive lesions are found in the central nervous system of chimpanzees with abortive or non-paralytic poliomyelitis following ingestion of infective material. In the human abortive disease late elevation of cerebrospinal fluid protein has been reported by Andelman and his associates.⁸ This protein rise, appearing two or three weeks after the acute infection, may indicate that some pathologic process has been in progress in the central nervous system even though no clinical evidence of it appeared. It is possible, therefore, that asymptomatic human carriers or persons with symptoms of mild abortive poliomyelitis who are excreting

* From the Section of Preventive Medicine, Yale University School of Medicine, New Haven, Conn. Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

virus in their stools may also harbor it in their central nervous systems.

In any event, because of its epidemiologic and clinical implications the recognition or at least the appreciation of abortive as well as non-paralytic and paralytic poliomyelitis is of importance. The clinician's course with respect to the abortive disease is clear. Although these cases cannot be reported as poliomyelitis since a definite diagnosis is not possible, all patients with brief febrile illnesses during an epidemic should be regarded with suspicion and treated more cautiously than usual, for there is no way of telling which patients will go on to develop frank poliomyelitis. In the beginning the physician may prefer not even to mention the diagnosis as a possibility, for families are prone to be apprehensive to the point of hysteria during a poliomyelitis epidemic and anything which minimizes commotion is desirable.

Non-paralytic and Paralytic Cases. There are several familiar patterns which the acute illness may take in both paralytic and non-paralytic types. The so-called "dromedary" or diphasic form is characterized by a first phase which is indistinguishable from the minor illness constituting the whole disease in the abortive form. The first phase may be followed by a few days of well being before the second phase is ushered in with a recurrence of first phase symptoms plus evidence of central nervous system involvement. Sometimes first and second phases are partially superimposed. Another situation, and the more common one, is that in which the first phase is so mild as to be missed or does not occur at all, and the acute illness develops with the appearance of central nervous system signs, sometimes after a vague non-febrile prodrome of several days' duration. Occasionally the onset may be prolonged with as many as ten days or more of prodroma without fever.

These various clinical forms of poliomyelitis are in some instances sharply defined and fairly easy to identify. Often, however, they overlap and merge so that diagnosis is anything but easy. Nor is it

always easy to decide whether to classify a case of non-paralytic or paralytic. For the question as to whether transient weakness of a few days' duration deserves the term paralysis is one on which physicians frequently disagree. Our practice is to designate those cases as paralytic poliomyelitis in which weakness or paralysis is demonstrable two weeks from the onset of second phase symptoms.

INCUBATION PERIOD

Since poliomyelitis has such a variable clinical pattern it is not surprising that the incubation period should appear to be variable, too. Figures varying from three to thirty-five days have been given⁹ but the average time is usually taken to be ten days. Inasmuch as we do not know what constitutes adequate exposure to the virus or exactly what form (or forms) such exposure may take, it is not possible to measure the incubation period with any degree of accuracy. The difficulty is enhanced by the fact that some patients have the biphasic course mentioned above and clinicians have not been consistent in designating the first day of the disease, whether it be the onset of the first or second phase. We have always considered the incubation period to be the time between exposure and the onset of first-phase symptoms, if such occur, in which case it is likely to average less than ten days. If no first phase occurs, one must date the incubation period from exposure to the onset of symptoms which may be ten days or longer.

THE HISTORY

An exploration into the epidemiologic circumstances often provides more of a lead as to diagnosis than do the actual clinical findings. Thus in the summer and during an epidemic the occurrence of mild, perhaps even non-specific symptoms compatible with early poliomyelitis are more suggestive of that diagnosis than the same symptoms encountered in the winter or in non-epidemic times. The probability of

poliomyelitis is enhanced if the patient is a child or a young adult or a young pregnant woman; if there has been other similar illness in the family, particularly in the young children; or if a definite case of poliomyelitis has occurred in the family.*

In eliciting the story of the onset of symptoms in a suspected case, particularly in a child, it is well to question specifically about a possible bout of *first-phase* symptoms, for often these are so mild as to be discounted by parents and their occurrence as long as a week before the appearance of more dramatic second-phase symptoms does not couple them with the latter in parents' minds. Listlessness, fever, headache, sore throat in the absence of an upper respiratory infection, anorexia, vomiting (rarely diarrhea), alone or in combination are the commonest symptoms in the first phase. Often they are of exceedingly short duration, a matter of a few hours; occasionally they last as long as two days but rarely more. The interval of well being before the onset of the second phase, if such occurs, varies from one to six or seven days, commonly three to four days.

The *second phase* (which more often occurs without an antecedent first phase) may appear abruptly or gradually over a period of several days. If the onset of symptoms is sudden, fever, headache and vomiting are most commonly encountered. The headache may be frontal, occipital or temporal; it is sometimes mild, often severe and bursting or pounding in type. A complaint of sore throat is not common as a second-phase symptom (although redness of the pharynx is the usual finding). Diarrhea has been described as a prominent feature in some

* There have been many observations on the familial epidemiology of poliomyelitis. Paul, Salinger and Trask⁶ concluded that "minor illnesses" which probably represent abortive poliomyelitis are four to six times commoner in the familial associates of a known case than in control groups in which no case has been observed. Casey, Fishbein and Bundesen¹⁰ have reported similar figures. Pearson et al.¹¹ and Wenner and Tanner¹² have isolated poliomyelitis virus from up to 80 per cent of the family contacts of known cases, and Zintek's study of a family epidemic¹³ illustrates the possible high incidence of infection in a family group with only one (or two) obvious cases.

epidemics but constipation seems to occur more often. These early symptoms are often accompanied or followed quickly by spontaneous pain in the extremities, both deep pain and hyperesthesias, and sometimes paresthesias. Soreness and stiffness of the neck and back are prominent early symptoms. The soreness of the neck is not always associated with the extensor muscle group; in some instances the flexors are painful, in which case the soreness is localized to the lateral neck, sometimes unilaterally, sometimes bilaterally. The soreness and stiffness of the back is usually present in the lumbar region but occurs also in the thoracic region and the patient then localizes it "between the shoulders." Severe lumbar back pain not associated with motion of the spine—in fact relieved by it—also occurs (especially in adults), as does severe abdominal pain which may be cramp-like or steady and involve any quadrant, although usually the lower ones. Flank pain (in the flank muscles) is sometimes mistaken for abdominal pain by the patient and the physician. Pain in the chest is more often localized to the lower part of the thorax; it may be deep pain aggravated by breathing and is commonly associated with hyperaesthesia and tenderness to pressure over the chest wall.

If the second-phase symptoms develop gradually as they frequently do in adults, they may do so over a period of several days or occasionally several weeks. Listlessness, slight and intermittent headache, anorexia, mild pains in the extremities, and again hyper- and paresthesias can occur before the onset of fever. Sometimes slight stiffness of the neck, back and hamstring muscles are present also for several days before the febrile period begins. This so-called "straggling" type of clinical picture may persist throughout the second phase, or the mild symptoms may suddenly be superseded by fever, vomiting, severe headache, peripheral pain and a sharp increase in stiffness of the neck and back.

Whether the onset of the second phase is sudden or gradual, a number of other

symptoms may be encountered. These include psychic reactions and transient changes in personality such as extreme irritability not associated with pain or hyperesthesia. The sensation has been described by patients as one of overpowering restlessness and hypersensitivity to external stimuli such as noise. Varying degrees of emotional instability and over-reaction often accompany this agitation. The emotional lability sometimes persists far into convalescence. Not infrequently a brief period (one day or less) of irritability is followed by more persistent listlessness, lassitude and even drowsiness and coma. Convulsions are rare but do occur. Dizziness, which is not true vertigo but a light-headedness is not an uncommon early symptom. Shaking chills are rare and more apt to occur in the bulbar form of the disease. Generalized tremulousness is also more common with bulbar poliomyelitis but occurs with other forms as well.*

In epidemic times, due to extensive publicity to acquaint parents with the symptoms of early poliomyelitis, physicians are more apt to be called to see patients before any weakness or paralysis develops. Because the early clinical picture can be so varied and even bizarre, the diagnosis may be suspected but not clear until the appearance of muscle stiffness and weakness. As long as fever persists one can expect paralysis to develop (or to extend). Weakness of an extremity is sometimes preceded by stiffness and twitching of the involved muscle groups but these may occur without subsequent paralysis. The story of falling when attempting to walk or sudden collapse of an extremity so that the patient falls to the floor unexpectedly is not uncommon. The patient may say that he then got up and walked off with no difficulty. A day later, however, the leg may be weak or paralyzed.

Although the onset of weakness or paralysis is common while fever is still

present, it often occurs as the fever begins to fall and concurrently with an improvement in the general clinical picture: the patient feels more alert, his headache, back and neck soreness are much improved and his appetite begins to return. He feels on the road to recovery but suddenly discovers that his limbs will not function properly.

VARIABILITY OF SYMPTOMS IN DIFFERENT AGE GROUPS

As in many infectious diseases the influence of age on symptomatology is important. A recent survey of several hundred poliomyelitis patients in various age groups during two large epidemics^{*14} has revealed that the clinical pattern in the non-paralytic and paralytic forms varies markedly in several respects with the age of the patient. Most striking differences were the following: (1) The diphasic, "dromedary" course was common in young children and rare in individuals over fifteen; (2) the onset of symptoms in young children was usually abrupt; in the older age groups it was often gradual and sometimes preceded by a relatively long prodromal period; (3) the time between the onset of preparalytic symptoms and the appearance of paralysis tended to be shorter in young children; (4) pain—both superficial and deep—was a more prominent feature of the disease in the older age groups than in young children.

The diphasic course, sometimes stated to occur in up to half the patients with signs of central nervous system involvement, diminished in frequency with increasing age of the patient as follows:

Age	No. of Cases	No. with Two Phases	Per cent with Two Phases
2-4	83	29	35
5-9	105	40	38
10-14	78	13	17
15-19	58	6	10
20+	59	7	12

Comparing combined age groups 2-4 and 5-9 with 15-19 and 20+, chi square = 24.14. $P = <0.001$.

* Since bulbar poliomyelitis is being discussed as a separate subject in this symposium, its special features will not be dealt with here.

* Detailed clinical histories were taken by one person from all the patients, or from the parents of the young children.

There was no striking preponderance of the diphasic course in the paralytic or non-paralytic groups.

Another difference was apparent in both paralytic and non-paralytic cases in the type of onset of "second"-phase symptoms, whether sudden or gradual:

Age	No. of Cases	Onset Sudden		Onset Gradual	
		No.	Per Cent	No.	Per Cent
2-4	83	70	82	13	18
5-9	105	86	82	19	18
10-14	78	44	56	34	44
15-19	58	27	47	31	53
20+	59	20	34	39	66

Comparing combined age groups 2-4 and 5-9 with 15-19 and 20+, chi square = 37.30. P = <0.001.

Spontaneous pain was encountered more frequently as the age of patients increased, and in individuals fifteen years and over it was striking. Severe, excruciating pain, sometimes as the first symptom and in the absence of fever, was a characteristic in the older age groups. This pain tended to appear suddenly during the night, most commonly in the low back but sometimes in the legs or flanks. In contrast to pain associated with stiffness of muscles it was relieved by motion and a number of patients told of having paced the floor all night in order to obtain relief. No counter-

Age	No. of Cases	Pain as a Presenting Symptom*		Pain during First Twenty-four Hours of Symptoms†	
		No.	Per Cent	No.	Per Cent
2-4	83	27	33	33	40
5-9	105	41	39	58	46
10-14	78	24	31	41	40
15-19	58	33	57	44	76
20+	59	37	63	45	76

Comparing combined age groups 2-4 and 5-9 with 15-19 and 20+, chi square = 16.37* and 32.71† P = <0.001.

part of this type of pain was encountered in young children.

Tabulating all complaints of pain, either superficial or deep (exclusive of headache) occurring during the first twenty-four hours of symptoms, the figures in the preceding table were obtained.

In addition to being more frequent in individuals fifteen and over, peripheral pain was often severe and protracted in the older age group, and mild and fleeting in young children.

Some of the variations in symptomatology characteristic of children and adults are illustrated by the following two cases:

Childhood Type. B. D., a two year old girl, was well until January 19th when she complained of sore throat and was noted to be listless and anorexic. These symptoms plus a low grade fever persisted through the following day but on neither day was she ill enough to remain in bed. On January 21st all complaints had disappeared and she seemed entirely well although not quite as peppy as usual. She played actively, however, and had no complaints during the following two days. At 2:00 A.M. on January 23rd she awakened suddenly crying and complaining that her head hurt. She slept again but awakened in the morning screaming with severe headache. Her fever was high and she was nauseated and refused food. If allowed to lie still, she was quiet and uncomplaining through the day, but any slight movement seemed to aggravate the head pain. At no time was there a complaint of pain in the extremities. She was seen by a physician who noted a red throat and prescribed sulfadiazine. She spent a restless night, awakening frequently. By morning the fever was still high, the neck was stiff and she seemed unable or unwilling to move her extremities or raise her head. Complete paralysis of arms and legs was evident during the course of the day. After admission to the hospital paralysis of the intercostal muscles and diaphragm developed and respirator treatment was necessary for a three-week period. Convalescence was slow; there was some return of function in all extremities, but severe residual paralysis were present several months after the acute illness.

Adult Type. J. H., a twenty-six year old newspaper reporter, on September 19th began

to feel cross and irritable which was unusual for him. This continued for three days when he noticed in addition the presence of an area of hyperesthesia over the right side of his low back; the skin felt "as though it had been bruised" but inspection by a member of his

hours walking around, crying with pain, exhibiting an emotionalism which was most unusual for him. By 3:30 P.M. the back pain was so agonizing that the physician was again called, morphine was again administered, and the patient slept until 7:00 P.M. On awakening

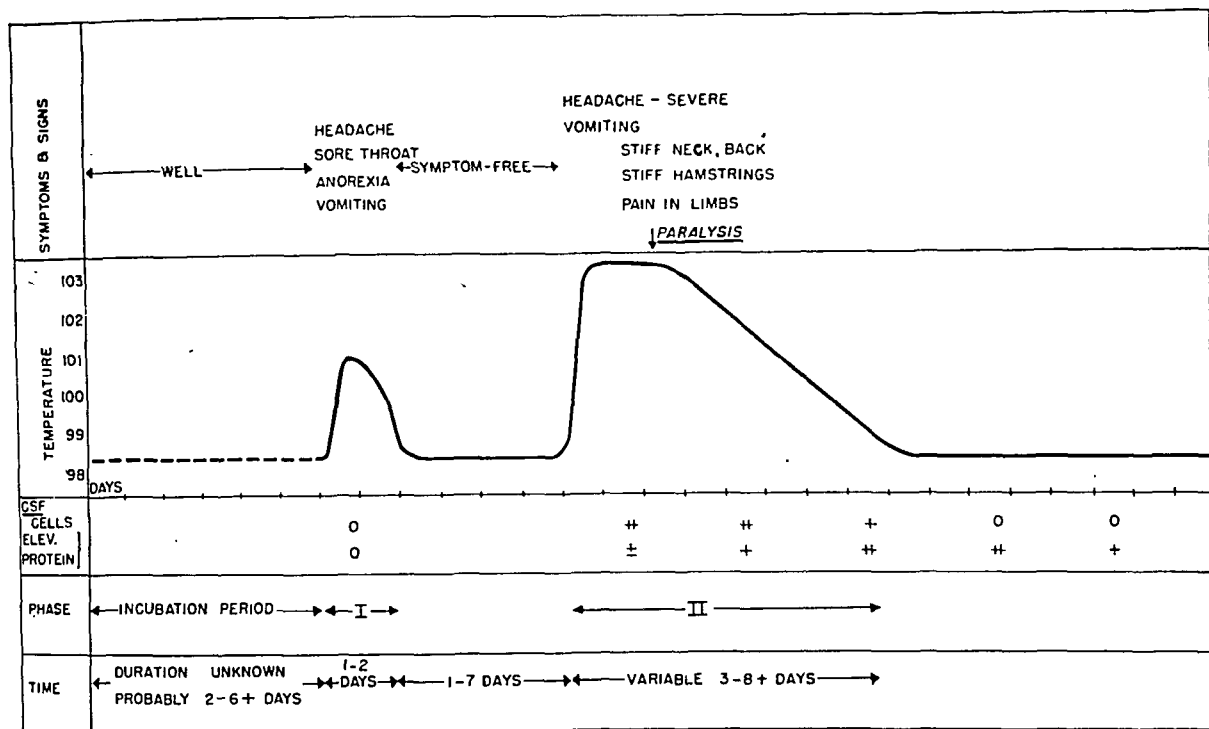


FIG. 1. Schematic diagram illustrating the clinical course of the "childhood type" of acute poliomyelitis.

family' revealed no skin lesions. Irritability and hyperesthesia continued for three days unaccompanied by other symptoms until September 25th when he felt tired and listless on awakening and noticed a slight headache and slight backache. His temperature was normal and he did not feel ill enough to remain in bed. He spent an active day, retired early and slept well until 3:00 A.M. when he was awakened by an excruciatingly severe pain around the middle of his body, most severe in the flanks and low back. The pain was so severe that he could not remain in bed but got up and paced the floor, which seemed to give some relief. At 3:30 A.M. a physician was called. A diagnosis of probable ureteral stone was made and he was given morphine, which enabled him to sleep until 7:00 A.M. On awakening the pain was still severe and by afternoon there was in addition severe headache, nausea and vomiting, and slight stiffness of the neck. The temperature remained normal. Throughout the day there was extreme restlessness and the patient spent

the same symptoms plus urinary retention were present, and hospitalization was recommended. The following morning, September 27th, a complete investigation of the genitourinary tract was undertaken but no ureteral stones were found. By afternoon the neck and back were stiffer and by the following day, September 28th, the legs were weak. A diagnosis of poliomyelitis was made and the patient was transferred to an isolation unit. At this time his temperature was 99°F., there was marked stiffness and retraction of the neck, marked stiffness of the back, and slight hamstring tightness, distended bladder, paralysis of both legs, weakness of the left arm, weakness of the intercostal muscles and diaphragm. Spinal puncture revealed 213 cells (84 per cent lymphocytes) and a + Pandy. He was placed in a respirator and on the following day, because of progressive bulbar signs, a tracheotomy was performed. His course continued stormy, with days of semi-coma and cyanotic periods. After several weeks, there was improvement in the bulbar signs but

the limbs remained essentially flail, and the patient was still in a respirator one month after onset.

Some of the differences in clinical pattern exhibited by these two patients are summarized in Figures 1 and 2. Young children

or no edema of the pharyngeal tissues. If and when the disease progresses, stiffness of the neck, back and hamstrings soon becomes very prominent and this condition is perhaps the most useful finding in establishing an early diagnosis. The stiffness

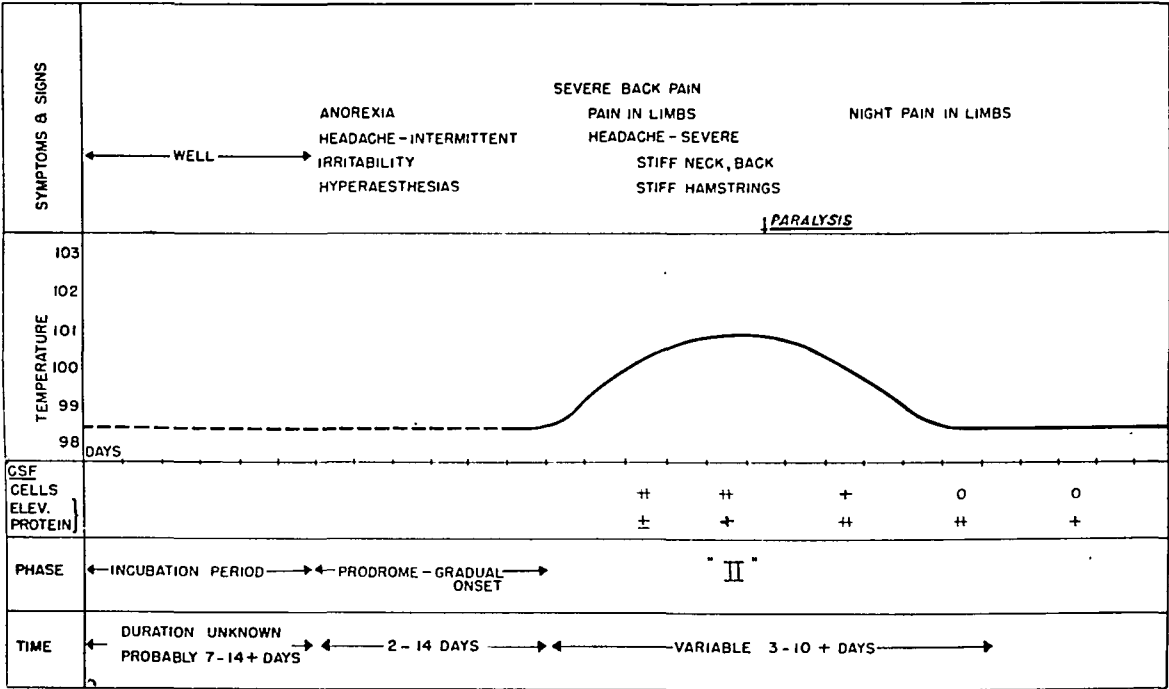


FIG. 2. Schematic diagram illustrating the clinical course of the "adult type" of acute poliomyelitis.

(Fig. 1) often have a diphasic course, a sudden onset of the second phase and a short preparalytic period. Young adults (Fig. 2), on the other hand, have a single phase but a more prolonged illness with gradual onset, several days of prodromal pain and a long preparalytic period. These patterns are by no means rigid; some adults have courses similar to that described as the childhood type while children sometimes exhibit courses more characteristic for adults.

PHYSICAL EXAMINATION

The patient in the first phase, or the abortive disease, presents no abnormalities on physical examination except listlessness, fever and some redness of the pharynx. In the beginning of the second phase the situation is similar: there is fever, a dusky red appearance to the pharynx but little

may be mild, merely a slight resistance to the last degree of flexion of the neck, or it may, rarely, be so marked as to present opisthotonus. Stiffness of the spine is best elicited by having the patient sit up in bed with the knees naturally flexed and asking him to "kiss his knees." If the back is supple, this is easily accomplished without discomfort. If the back is stiff, however, it may be difficult or impossible to perform, and attempts to do so will be accompanied by considerable pain. In this case the spine sign is positive. If the back is flattened and rigid, the patient may not be able to sit naturally at all but will support himself on his two outstretched hands, his trunk tilted backwards, i.e., in the "tripod position" which is also a characteristic sign. Tightness of the hamstring muscles and resistance to extension of the leg are very common. Other muscles, including the calf

muscles and those of the upper extremities, may also exhibit stiffness and tightness; wherever this stiffness and tightness exist the muscles are apt to be sore and any attempted motion painful. The mechanism of the stiffness is not clearly understood, nor is it apparent why it persists undiminished in certain patients long after the acute illness has subsided, and sometimes in the absence of any muscular weakness.

Another sign which is perhaps less well known but was described at least thirty-five years ago¹⁵ is "head drop." Dr. A. L. Hoyne, whose name is associated with this sign, has used it effectively and has emphasized its value. It is elicited by having the child lie on its back, placing one's hands beneath his shoulders and so lifting him up from the bed. In the normal child the head follows along in a plane with the body as it is raised but in poliomyelitis (even in its earliest stages) the head falls back limply in a position of hyperextension. Although this sign is not specific—it occurs in children severely ill with any prostrating disease including pneumonia and meningitis—in the obvious absence of such disease it is a useful sign which suggests poliomyelitis.

Although there may be stiffness of the back, neck and hamstrings, the reflexes in the early stages may be normal and active. In the non-paralytic disease they usually remain so. When changes begin to appear, characteristically there is first an irregular shift from normal to hyperactive, and then sudden (and sometimes transient) shifts to diminished or absent reflexes. Usually the appearance of reflex changes precedes the advent of weakness or paralysis by twelve to twenty-four hours, and may therefore herald that event. The superficial reflexes are the first to go: the abdominals, cremasteric and spinal reflexes. The latter, which are normally present segmentally from the upper back down to and including the gluteal region, although not so widely tested as the abdominals, are of similar significance; sometimes they disappear before the abdominals. The site of the absent superficial reflex is often of prognostic

importance; thus if the right lower abdominal reflex disappears, one may expect to find some weakness of the right lower extremity the following day.

Changes in the deep reflexes have also a prognostic value. A diminished patellar response on one side, or an exaggerated one, may point to possible subsequent development of weakness on that side. As weakness and paralysis increase there is a progressive loss of reflexes, and a patient seen in the stage of severe paralysis of all extremities may have no demonstrable reflexes,"superficial or deep.

The periodic examination for muscle power need not and should not be exhaustive in the acute stage of the disease but it is valuable to have a record of the general state of the muscle groups as a base line. All patients in whom there is progressing muscle weakness require observation frequently for evidence of diminished excursions of the intercostals and diaphragm.

CLINICAL LABORATORY FINDINGS

Spinal Fluid. The most valuable laboratory test in the diagnosis of poliomyelitis is the examination of the spinal fluid. If the total white cell count is elevated above 8 to 10 cells, and the protein above 35 to 45 mg. per 100 cc., the diagnosis in a suspicious case is more likely. Although spinal fluid abnormalities are usual in poliomyelitis, one cannot rely on a negative test to rule out the diagnosis, because if the patient has the abortive form or is in the first phase of a "dromedary" course, a negative spinal fluid is to be expected. If he has non-paralytic or even paralytic poliomyelitis, his spinal fluid may still be normal, especially if he is seen on the first day of symptoms. Occasional patients with the non-paralytic or paralytic form of the disease have persistently normal spinal fluid cell counts; in one series of cases the figure given was 12 per cent.¹⁶ Fraser¹⁷ cited a paralytic case which was fatal several hours after a spinal tap revealed a normal fluid and we also have seen a negative fluid in a fatal case proved at autopsy.

Although spinal fluid findings are not diagnostic (or prognostic) in poliomyelitis, certain features are characteristic at various stages of the disease. Since 1912¹⁵ it has been emphasized that (1) the cell count is highest during the first week of the disease in the preparalytic and paralytic stages; (2) the predominant cell type is almost always the mononuclear although often early in the disease the polymorphonuclear form predominates; (3) the protein is low and often normal during the first week but rises during the second and third weeks, remains up through the fourth week, gradually decreasing to normal by the fourth to tenth week. Thus the protein is still elevated and often still rising while the cell count has returned to normal. Recent studies have confirmed and extended these early findings¹⁸ and it is apparent that the CSF picture in *late* poliomyelitis resembles that of the Guillain-Barré syndrome and diphtheritic polyneuritis.

Blood. There is no consistent change in the blood picture. As a rule the white cell count is normal or moderately elevated (10 to 15,000) with a slight shift in the differential count and relative lymphopenia. If the patient is dehydrated, there may be a high hematocrit and a more elevated white cell count. Rapid erythrocyte sedimentation rates have recently been reported to occur in about half the patients tested.¹⁹ At present there is no serologic test available which is diagnostic for poliomyelitis.

Urine. Routine urinalysis reveals no abnormalities. Watson and his colleagues²⁰ have described an increased excretion of coproporphyrin III in acute poliomyelitis.

DIFFERENTIAL DIAGNOSIS

During an epidemic certain diseases must be considered, especially in some areas. In the western part of the United States and particularly in California, the *arthropod-borne encephalitides* are the most important. Since the seasonal incidence and clinical picture of eastern and western equine encephalomyelitis and St. Louis encephalitis may be indistinguishable from

that of poliomyelitis, the final diagnosis of these diseases rests on serologic evidence. Clinical signs which may be of help in differentiation include the greater tendency for patients with the encephalitides to show sustained high fever, convulsions, ophthalmoplegia, and less commonly than poliomyelitis, paralysis of the limbs.

Rocky Mountain spotted fever and *endemic typhus* are summer diseases (depending somewhat on the part of the United States and the time at which the vectors flourish) and can simulate the clinical picture of poliomyelitis. In their early stages fever, headache, severe muscle pain, hyperesthesias, restlessness, insomnia and stiff neck may all be present for several days before the rash appears to clarify the diagnosis.

It is now apparent that *mumps meningo-encephalitis* may occur in the absence of parotitis, and may have a clinical picture similar to that of non-paralytic poliomyelitis. If this disease is suspected, it is important to ascertain whether classical mumps cases exist in the patient's family or community. There is no clinical sign which can be relied upon to differentiate aseptic meningitis from non-paralytic poliomyelitis, but both mumps and lymphocytic choriomeningitis can eventually be diagnosed by serologic means if acute and convalescent sera are available.

Mention has already been made of the patient with severe back pain whose illness is mistaken for kidney disease. Severe abdominal pain, which may shift from the epigastrium to the right lower quadrant and may be associated with nausea and vomiting, sometimes results in the admission of a poliomyelitis patient to a surgical service where appendicitis is suspected and an appendectomy may be performed before the correct diagnosis becomes apparent. *Epidemic pleurodynia* or Bornholm disease, which is also a summer disease, is occasionally mistaken for poliomyelitis; the rapid subsidence of fever and chest pain in twenty-four hours, without stiffness of muscles, distinguish it however.

The *Guillain-Barré syndrome* or infectious

polyneuritis seems to appear in the course of every epidemic of poliomyelitis. It should be entertained as a possibility in patients with paralysis whose spinal fluid *early* in the acute disease reveals a normal cell count but an elevated protein content. The clinical features which distinguish it from poliomyelitis are the symmetrical distribution of paralyses (particularly facial diplegia), the frequent occurrence of sensory loss and the absence of muscle tightness and pain.

Various infections including streptococcal sore throat, retropharyngeal abscess and the exanthemas are sometimes accompanied by transient meningismus which may be confusing. Other conditions which should be kept in mind and ruled out are the post-exanthem encephalitides, transverse myelitis, post-diphtheritic polyneuritis, purulent meningitis, tuberculous meningitis, as well as the more remote possibilities of rheumatic fever, trichinosis and osteomyelitis.

MEDICAL TREATMENT

At the present time there is no specific treatment available for poliomyelitis. None of the antibiotics or sulfonamide derivatives which have been tried has had any effect in destroying the virus or controlling its spread in the body. At one time it was believed that convalescent serum was a valuable specific form of therapy. However, no controlled trials have been reported which would support this view; in fact the recent study by Bahlke and Perkins,²¹ in which large doses of gamma globulin were given to alternate patients in the preparalytic stage without demonstrable effect on their subsequent courses, establishes the ineffectiveness of such therapy as far as adult serum is concerned. Another point which militates against the use of serum is the evidence that patients may already have specific antibodies against their own strain of virus by the time they are admitted to the hospital.²²

Since there are no specific therapeutic agents available, medical management comes down to general supportive measures

and the anticipation and handling of complications.

Hospitalization. The tendency at present is to treat all patients in whom a definite diagnosis has been made in the hospital. This is probably wise since there is such uncertainty as to the future course in all early cases. However, the decision as to which cases are to be hospitalized and which may be treated at home will vary in different places and at different epidemics, depending on the local facilities available. A special isolation hospital is not necessary for general hospitals can care for poliomyelitis patients and should accept their community responsibility to do so. In the transportation of the patient to the hospital, care should be exerted that the trip involves a minimum of exertion and trauma.

In the hospital, management of the patient with poliomyelitis has become a task involving the services of a team of specialists. During the acute illness it has proved most satisfactory to have his care in the charge of the internist or pediatrician, with specialists in orthopedics and physical medicine acting as consultants, directing the special forms of treatment which are their province. Depending on the condition of the patient rather than on any arbitrary time designated as the end of the isolation period, the responsibility is transferred to the orthopedist or the specialist in physical medicine for convalescent and late treatment.

General Measures. Early bed rest is important for all patients whether at home or in the hospital. There seems little doubt that it is one of the most important therapeutic and preventive measures, especially after the onset of the preparalytic phase. Russell's recent study²³ suggests that there is a close correlation between the degree of physical activity in the early preparalytic phase and the final outcome in terms of severity of paralysis. Such correlation has long been postulated on the basis of clinical experience. The history of violent exercise immediately preceding the onset of paraly-

sis is not an uncommon one, and this fact coupled with experimental evidence that virus concentration in the anterior horn cells is high at least one day before paralysis appears²⁴ has been interpreted as indicating that physical activity may be one of the mechanisms which upsets host-virus equilibrium and precipitates irrevocable injury to the cells of the central nervous system. The evidence²³ that bed rest (i.e., avoidance of any physical activity) may be a factor which contributes to the arrest of the disease in the preparalytic phase is of great therapeutic importance. Bed rest for a few days following the abortive disease, and certainly a longer period following the mild non-paralytic type, is strongly recommended for rest may be one factor in preventing the late paralyses which sometimes occur.

Orthopedists recommend that a firm hard bed be provided from the beginning, particularly for patients with marked muscle tightness and paralyses. The bed should be fitted with a footboard placed several inches beyond the mattress end, allowing room for the heels or toes when the patient lies supine or prone. The footboard also serves to protect the extremities from the pressure of bed-clothing and allows proprioceptive reflexes to be stimulated when the feet rest against it. If the legs are weak, the knees should be supported in a slightly relaxed position; weak arms should be in external rotation alongside the body but not against it. If the patient is acutely ill or irrational, it will obviously not be possible to keep him in this position, but the sooner it can be achieved the better.

Purely medical aspects of treatment cannot of course be separated from other forms of therapy. The maintenance of good morale is an important feature which is apt to be overlooked in the stress of an epidemic when acute medical emergencies are at hand. Poliomyelitis, perhaps more than any other disease in our time, provokes fear and terror in the public mind. The patient whether child or adult, may therefore enter the hospital in a state of extreme apprehension. He requires continuous help and reassurance to enable him to adjust

to his illness and perhaps to a permanent physical handicap. If this help can be given from the beginning, there is less danger of the later development of neurotic fears and dependencies which in addition to their psychiatric implications may interfere with the achievement of maximum physical improvement.²⁵

Preparalytic Stage (and Non-paralytic Cases). In mild non-paralytic cases with little fever and minimal stiffness no treatment other than bed rest, light diet and adequate nursing care is necessary. In the more severely ill patient who has high fever and is dehydrated, parenteral fluids and salt are indicated.

Sedation and relief of pain are often pressing problems in the early acute disease. Relief of pain is best accomplished by the intermittent application of hot moist packs according to Miss Kenny's technic,²⁶ a subject which is reviewed in another article in this symposium. Hot baths may also be used effectively, especially in small children. Whenever hot packs or hot baths are used, salt tablets should be given to prevent chloride depletion which results from excessive salt loss in perspiration.

The response to the common analgesics is not very satisfactory but aspirin, codeine or demerol may be used. Often, if pain is relieved by means of hot packs and drugs, the patient will fall asleep easily and sedation will not be necessary. This is a desirable result for the danger of aggravating incipient or actual respiratory difficulty makes it necessary to use sedatives cautiously. Some physicians believe, however, that the relatively great physical activity of the restless, sleepless, patient tossing about the bed all day and all night represents a danger in possibly precipitating paralysis, and adequate sedation should therefore be given if there is no obvious respiratory embarrassment.

In recent years several drugs have been advocated for the relaxation of muscle tightness and relief of pain. Kabat and Knapp²⁷ introduced prostigmine in 1943 and it has received extensive clinical trial, with variable results.^{28,29} Ransohoff³⁰ has

recommended curare enthusiastically but not all are agreed as to its benefits³¹ and it has been found to be a drug of considerable potential danger. Cole³² states that none of the drugs has been found to be as effective as the more tedious and cumbersome method of hot packs, and none has therefore come into general use.

Paralytic Stage. What has been said of the care indicated in the pre-paralytic phase applies equally to the early paralytic. The problem of the relief of pain may continue for some time. Although the patient is comfortable during the day, he may suffer *night pain*, severe, deep, aching pain in the weakened or paralyzed back or extremities, which persists sometimes for weeks. This pain often defies every form of treatment which may be tried, including continuous hot packs, analgesics and sedatives.

Complications. Certain complications require special treatment. *Urinary retention* is common in patients with severe involvement of the lower extremities. Before resorting to catheterization an adequate trial of drug therapy should be given. So far, the parasympathomimetic drug, furfuryl trimethylammonium iodide ("furmethide") has proved the most efficacious if given in adequate dosage.³³ If there is no response to drugs, catheterization will be necessary. It may be required for several days, in which case prophylactic sulfadiazine should be given. In most instances retention lasts only a few days and there is no further difficulty. For this reason an indwelling catheter is rarely indicated and never until after several days' trial of drugs and repeated catheterization have failed. The objection to an indwelling catheter is that it tends to prolong the period of retention and the eventual risk of infection is therefore increased.

Atony of the gastrointestinal tract is a common occurrence, especially in patients with paralysis of the lower extremities. Prostigmine in small doses produces contraction of the bowel and relief of abdominal distention and discomfort. The normal tone of the gastrointestinal musculature usually returns spontaneously within a few days.

Respiratory failure is the most serious complication in poliomyelitis. It may be of two types (1) central, which occurs in bulbar poliomyelitis and results from involvement of the respiratory center; and (2) peripheral, as a result of involvement of the segments controlling respiratory muscles, the intercostals and diaphragm. Both types may be seen in the same patient at the same time. The extremely complex mechanisms of respiratory dysfunction which result have been studied in detail by Elam and his associates.³⁴

The treatment of respiratory failure of the central type is a problem in the management of bulbar poliomyelitis and is discussed elsewhere in this symposium. In following a patient with spinal poliomyelitis who is beginning to have difficulty in breathing it is wise to have a respirator at the bedside ready for use, for sudden changes in the character of the breathing may necessitate immediate artificial respiration. If there is doubt about the function of the diaphragm, fluoroscopy of the chest is helpful in determining its degree of motion. Not infrequently the first signs of trouble are due not to actual weakness of the respiratory muscles but predominantly to their being "in spasm," i.e., tight and stiff, just as other muscles may be. The first form of treatment to be tried, therefore, is hot moist packs to the chest, applied intermittently for twenty- to thirty-minute periods. In some instances the respiratory exchange (which can be followed easily by listening over the mouth or nose with a stethoscope) improves and the patient relaxes. In others, in whom progressive muscle weakness is occurring, there may be no improvement but a progression of symptoms and signs: more and more feeble respiratory excursions, increasingly rapid pulse, cyanosis and apprehension. In such a situation respirator treatment will be necessary.

Once in a respirator the patient requires constant attention. If he is severely ill or comatose, a Levine tube for feeding will be necessary. Intravenous fluids are frequently required. Sometimes considerable explana-

tion may be necessary before the patient can be persuaded to coordinate his breathing with the respirator and not to fight the machine. If there is some element of central respiratory failure as well as respiratory muscle paralysis, the respiratory center may be sending out irregular impulses which interfere with the rhythmical mechanical respirations induced by the respirator. In such instances curare has been employed to block the response of the respiratory muscles to the irregular stimuli issuing from the respiratory center, thus allowing the respirator to "take over." Usually it is necessary to give only one dose following a test dose, for once the respirator rhythm is established it continues reflexly.

From now on many possible complications may occur. It is useful to have a stethoscope taped over the P.M.I., the ear pieces extending to the outside, in order to record the heart rate at frequent intervals. Prophylactic penicillin may be given to protect against respiratory tract infection. Continuous intranasal oxygen is indicated if the color is poor or if there is any evidence of central respiratory failure. (If the patient has had a tracheotomy, oxygen is given through the tracheal tube.)

Pulmonary atelectasis is a complication to which respirator patients are particularly prone. It can be prevented to some extent by the use of oxygen under positive pressure either continuously or intermittently by mask. When atelectasis occurs, bronchoscopy and removal of the plug of secretions may be a life-saving measure. Not infrequently patients develop recurrent attacks of cyanosis but on bronchoscopy no plug is found. Patchy peripheral atelectasis is a possible explanation of these episodes; they may be difficult to control but positive pressure oxygen seems to reduce the frequency of their occurrence.

The problem of dispensing with the respirator as early as possible is important since the machine tends to suppress the normal mechanism of breathing, and the patient literally forgets how to breathe by himself. Also, the longer he is in a respirator the more difficult the process of wean-

ing him away from it becomes. The use of the oximeter, described by Millikan,³⁵ has proved of benefit in enabling clinicians to follow the progress of the patient with respect to his respiratory function. This instrument is attached to the pinna of the ear and readings of the relative saturation of oxyhemoglobin in arterial blood are obtained. The level can be followed when the patient is removed from the respirator, a fall below a certain level being an indication for him to be returned to the machine. Usually the time out of the respirator can be increased gradually, day by day, until the machine can be abandoned entirely.

PROGNOSIS

As far as the acute stage of poliomyelitis is concerned, the subject of prognosis can be summarized briefly: (1) Early in the course no prediction can be made. (2) As long as fever persists there is a possibility that paralysis may develop or extend; once the temperature has returned to normal the development of paralysis is rare. (3) The mortality rate varies considerably in different epidemics but is usually 5 to 8 per cent. It is greatest in the bulbar form of the disease and in those with peripheral respiratory failure. It varies also with increasing age of the patient, being considerably higher in adults than in children.

CLINICAL IMMUNITY

It has usually been assumed that one attack of poliomyelitis confers solid immunity to the disease. There is evidence that chimpanzees, who seem to resemble humans in their response to infection with the virus of poliomyelitis, can be infected repeatedly with different strains of virus but are not subject to reinfection with the same strain.³⁶ In the human disease authenticated second attacks have been reported rarely but they probably occur more often than they are reported. Fischer and Stillerman³⁷ have raised the question as to whether the low morbidity rate in poliomyelitis would not make the incidence of second attacks rare even if no immunity occurred following the disease. In the 1935

New York City epidemic they observed four second attacks, a rate of 2 per thousand, which was within the limits of expectancy if no immunity resulted from a previous attack. However, these figures were not based on age specific rates and cannot therefore be taken as final. Nevertheless, increasing evidence of the widespread distribution of virus during epidemics suggests that reinfection with poliomyelitis virus may occur more often than has been supposed, but the reinfection usually remains at the subclinical level.

REFERENCES

1. PAUL, J. R. and TRASK, J. D. Observations on the epidemiology of poliomyelitis. *Tr. Coll. Physicians, Philadelphia*, 54: 158, 1932.
2. SWEETNAM, W. P. Epidemiology of the 1947 outbreak of poliomyelitis in Eccles. *Brit. M. J.*, 1: 1172, 1948.
3. THOMPSON, A. W. S. A contribution to the epidemiology of poliomyelitis in New Zealand. Dept. of Health. Annual Report of the Director-General of Health. New Zealand, 1948.
4. MELNICK, J. L. Poliomyelitis virus in urban sewage in epidemic and non-epidemic times. *Am. J. Hyg.*, 45: 240, 1947.
5. PAUL, J. R., SALINGER, R. and TRASK, J. D. "Abortive" poliomyelitis. *J. A. M. A.*, 98: 2262, 1932.
6. DRAPER, J. In Nelson's Loose Leaf Living Medicine. Chap. 31, p. 67. New York, 1926. Thos. Nelson and Sons.
7. BODIAN, D. and HOWE, H. A. Non-paralytic poliomyelitis in the chimpanzee. *J. Exper. Med.*, 81: 255, 1945.
8. ANDELMAN, M. B., FISHBEIN, W. I., CASEY, A. E. and BUNDESEN, H. N. Spinal fluid protein in the retrospective diagnosis of sub-clinical poliomyelitis. *South. M. J.*, 39: 706, 1946.
9. HORSTMANN, D. M. and PAUL, J. R. The incubation period in human poliomyelitis and its implications. *J. A. M. A.*, 135: 11, 1947.
10. CASEY, A. E., FISHBEIN, W. I. and BUNDESEN, H. N. Transmission of poliomyelitis by patient to patient contact. *J. A. M. A.*, 129: 1141, 1945.
11. PEARSON, H. E., BROWN, G. C., RENDTORFF, G. M., RIDENOUR, G. M. and FRANCIS, T. Studies of the distribution of poliomyelitis virus. *Am. J. Hyg.*, 41: 188, 1945.
12. WENNER, H. A. and TANNER, W. A. Widespread distribution of poliomyelitis in households attacked by the disease. *Proc. Soc. Exper. Med. & Biol.*, 66: 92, 1947.
13. ZINTEK, A. R. The rapid infection of a family after introduction of poliomyelitis virus. *Am. J. Hyg.*, 46: 248, 1947.
14. Yale Poliomyelitis Study Unit. Unpublished observations.
15. PEABODY, F. W., DRAPER, G. and DOCHEZ, A. R. A clinical study of acute poliomyelitis. Monograph of the Rockefeller Institute for Medical Research, No. 4, 1912.
16. MEALS, R. W. and BOWER, A. G. Poliomyelitis. *J. Lab. & Clin. Med.*, 17: 409, 1932.
17. FRASER, F. R. A study of cerebrospinal fluid in acute poliomyelitis. *J. Exper. Med.*, 18: 242, 1915.
18. GAMMON, G. D., TODD, J. C., LUCCHESI, P., LA BOCGETTA, A., CHANCE, B., SILVERSTEIN, A. and SUNDERMAN, F. W. The spinal fluid in poliomyelitis. *Arch. Neurol. & Psychiat.*, 59: 551, 1948.
19. HARTMAN, T. L. and WEINSTEIN, L. Erythrocyte sedimentation rate determinations in poliomyelitis and other infections of the central nervous system and meninges. *J. Pediat.*, 33: 462, 1948.
20. WATSON, C. J., SCHULZE, W., HAWKINSON, V. and BAKER, A. B. Coproporphyrinuria (type m) in acute poliomyelitis. *Proc. Soc. Exper. Biol. & Med.*, 64: 73, 1947.
21. BAHLKE, A. M. and PERKINS, J. E. Treatment of preparalytic poliomyelitis with gamma globulin. *J. A. M. A.*, 129: 1146, 1945.
22. HAMMON, W. McD. and ROBERTS, E. Serum neutralizing antibodies to the infecting strain of virus in poliomyelitis patients. *Proc. Soc. Exper. Med. & Biol.*, 69: 256, 1948.
23. RUSSELL, W. R. Poliomyelitis. The preparalytic stage, and the effect of physical activity on the severity of paralysis. *Brit. M. J.*, 2: 1023, 1947.
24. BODIAN, D. and CUMBERLAND, M. The rise and decline of poliomyelitis virus levels in infected nervous tissue. *Am. J. Hyg.*, 45: 226, 1947.
25. EBAUGH, G. F. and HOEKSTRA, C. S. Psychosomatic relationships in acute anterior poliomyelitis. *Am. J. M. Sc.*, 213: 115, 1947.
26. POHL, J. F. and KENNY, E. The Kenny Concept of Infantile Paralysis and Its Treatment. Minneapolis, 1943. Bruce Publishing Co.
27. KABAT, H. and KNAPP, M. E. Use of prostigmine in the treatment of poliomyelitis. *J. A. M. A.*, 122: 989, 1943.
28. BRAINERD, H., KATZ, H. J., ROWE, A. P., JR. and GEIGER, J. C. The clinical manifestations of poliomyelitis. Treatment with neostigmine and the Kenny method. *J. A. M. A.*, 128: 718, 1945.
29. EVELETH, M. S. and RYAN, A. J. Prostigmine in acute anterior poliomyelitis. *Yale J. Biol. & Med.*, 17: 351, 1944.
30. RANSOHOFF, N. S. Curare in the acute stage of poliomyelitis. *J. A. M. A.*, 129: 129, 1945.
31. ROSENBERG, D. and FISCHER, A. E. Curare in the acute stage of poliomyelitis. *Pediatrics*, 1: 648, 1948.
32. COLE, W. H. Present methods in treatment of infantile paralysis. *Postgrad. Med.*, 4: 185, 1948.
33. LAWSON, R. B. and GARVEY, F. K. Paralysis of the bladder in poliomyelitis. *J. A. M. A.*, 135: 93, 1947.
34. ELAM, J. O. Physiological management of respiratory dysfunction in poliomyelitis. Round table discussion—poliomyelitis. *Pediatrics*, 1: 691, 1948.
35. MILLIKAN, G. A. The oximeter, an instrument for measuring continuously the oxygen saturation of arterial blood in man. *Rev. Scient. Instruments*, 13: 434, 1942.
36. MELNICK, J. L. and HORSTMANN, D. M. Active immunity to poliomyelitis in chimpanzees following subclinical infection. *J. Exper. Med.*, 85: 287, 1947.
37. FISCHER, A. E. and STILLERMAN, M. Does an attack of acute anterior poliomyelitis confer adequate immunity? Report of 4 second attacks in New York City in 1935. *J. A. M. A.*, 110: 569, 1938.

Moist Heat in the Treatment of Poliomyelitis*

WILLIAM T. GREEN, M.D. and THOMAS GUCKER, III, M.D.

Boston, Massachusetts

MOIST and dry heat have apparently been advocated for the treatment of poliomyelitis from the time the disease has been recognized. Recently the use of hot packs has been so emphasized that they have in the popular mind come to indicate a method of treatment from which miraculous effects are to be expected. In truth they have no such effects although the use of moist heat and hot packs represents an adjunct which is distinctly helpful.

Treatment in poliomyelitis is adjusted to the problem presented by the individual patient and to the stages of the disease, whether in reference to the use of moist heat or other factors. For our purposes the disease may be classified as follows: (1) The acute stage which represents the febrile illness; (2) the convalescent stage which follows the acute illness and may be said in a general way to start forty-eight hours after the febrile illness and extend for approximately sixteen months and (3) the chronic stage. The convalescent stage may be subdivided into: (1) the sensitive phase when muscle sensitivity and spasm are present and (2) the asensitive phase when significant sensitivity and spasm have disappeared.

This discussion of moist heat primarily will be concerned with its use during the latter part of the acute illness and the sensitive phase of the convalescent stage.

PROBLEMS PRESENTED BY THE DISEASE

Before discussing the place of moist heat in treatment it is well to consider some of the manifestations of the disease and certain of the objectives of treatment. In the paralytic phase of the acute stage and in

the sensitive portion of the convalescent stage the disease tends to be especially crippling and deforming since the findings are those of a combination of flaccid paralysis and of sensitivity and spasm of the muscles. This combination tends to be particularly deforming, in that the paralyzed muscles cannot control the part and the muscles which are in spasm tend to draw the part into deformity. Gravity often accentuates these bad positions. Since the muscles are sensitive to stretching and handling, the deformed positions tend to be maintained unless counter measures are taken. As time goes on these deformities become fixed due to secondary adaptation of the muscles to their shortened length. The longer a part is left in a fixed attitude the more difficult it is to get it out of this position. Very similar phenomena were demonstrated experimentally in animals by Ranson and Sams¹ as a fundamental neurologic mechanism occurring in conditions other than poliomyelitis. They proposed the term "hypertonic contracture" to describe the state of muscle spasm and applied the term "myostatic contracture" to the secondary shortening of the muscles.

Patients show great variability in the degree of sensitivity and spasm, as do the individual muscles in the same patient. Certain muscle groups are more likely to show spasm of a significant clinical degree than others. Particularly is this true of the posterior muscles of the neck, back, thigh and calf and the adductor muscles of the arm. Those muscles which would show spasm as a result of meningeal irritation from any cause are ordinarily the first to show spasm in poliomyelitis. Furthermore, it is noteworthy that the pain and sensitivity

* From the Harvard Medical School, and The Orthopedic Dept., The Children's Medical Center, Boston, Mass.

frequently do not parallel the amount of demonstrable spasm. Those patients with severe pain and sensitivity do not necessarily have more tightness of muscles than others. The duration of the sensitivity varies widely. Sometimes significant spasm and sensitivity are minimal after a few days. More often it exists for two to three weeks and occasionally it is present for a much longer period. In part at least this duration has a specificity for the individual patient.

Although the cause of paralysis in poliomyelitis is well accepted the explanation of pain and spasm remains controversial. Years ago involvement of the posterior ganglia was considered to be a likely cause.² More recently pathologic studies³ have led to the proposal of an hypothesis that the spasm is due to involvement of the internuncial cells in the spinal cord. Still others^{4,5} have suggested that involvement of the reticular formation and vestibular nuclei in the brainstem may give rise to muscle spasm.

Actually many of the phenomena in the general field of pain are imperfectly understood. The reaction in an individual which is described as pain can be elicited by numerous agents and conditions through a complex physiologic and psychologic mechanism. Studies⁶ of the factors involved in the production of pain in contracting skeletal muscle, particularly in angina pectoris and intermittent claudication, have suggested the presence of a chemical substance which others⁷ have concluded is related to lactic acid produced in the metabolism of muscle. This presumably stimulates pain receptors when it reaches sufficient concentration. Ischemia, through vasoconstriction, favors the concentration of such a substance and vasodilatation alleviates pain by an increase in blood flow which reduces the concentration. The relation of pain in poliomyelitis to ischemia of the muscles has been proposed⁸ but recent studies by Gucker, Green and Anderson⁹ of the skin and calf muscle temperatures in paralyzed and unparalyzed extremities of

patients in the early stage of poliomyelitis have demonstrated that there is no primary vasoconstriction as determined by this method. Little evidence exists to substantiate a chemical substance theory in explaining the pain and sensitivity of acute poliomyelitis. Clinically, the "spasm" seems to be, at least, very similar to so-called reflex muscle spasm which accompanies pain arising in such conditions as peritoneal irritation, inflammation of joints and fractures.

Whatever their pathogenesis the pain, muscle sensitivity and spasm are significant factors in the disease although the prognosis depends essentially upon the degree and distribution of the paralysis. If there is no detectable paralysis, the spasm and sensitivity are of little consequence except to make the patient more or less comfortable. However, sensitivity and spasm in a patient who has paralysis contribute to deformity, impair muscle function during the sensitive stage and upset reciprocal innervation. Deformities not only disturb function through mechanical abnormality but inhibit the recovery and function of muscles which are maintained in the stretched position. Furthermore, in the growing child deformities once established are often progressive.

It is not within the scope of this article to discuss the general problem of therapy in poliomyelitis. It is our purpose to consider only those aspects which are related to the use of moist heat. Some of the objectives of therapy are the relief of pain, prevention and correction of deformities and development of full ranges of motion as early as this can be done comfortably. It is in this sphere that the use of moist heat seems to be helpful since there is no evidence that its use affects the degree of paralysis.

PHYSIOLOGIC ACTION OF MOIST HEAT

The soothing effect of heat upon pain from various causes is well known. In a painful joint with muscle spasm heat is of assistance in relieving the pain, reducing spasm and promoting motion. The exact

mechanism by which heat accomplishes this is not certain.

According to Krusen,¹⁰ extremely hot or cold water increases the sensitivity of cutaneous nerve endings whereas prolonged warm or cool baths diminish sensibility and relieve pain. A warm bath is more effective and acts as a depressant. Bazett¹¹ states that the superficial capillaries, venules and arterioles dilate in response to heat, resulting in an increase in the rate of blood flow which intensifies the thermal conductivity of the tissues. This increased circulation tends to distribute the heat throughout the body thus hindering a rise in the local temperature. Significant heating of the deeper tissues occurs in the specific area to which the heat is applied. Application of local heat elevates the temperature of the muscle to a very considerable degree.¹² One of us (T. G.) has shown that this is accomplished whether hot packs, luminous heat or tubs are used. With hot packs, the rise in skin temperature is abrupt whereas with luminous heat it is more gradual. Comparable increases in the deep muscle temperature occur, however, by both methods.

If a pack at a temperature as high as can be comfortably tolerated is applied to the lower leg of a patient in a room of ordinary temperature, there is usually a rise of 6 to 10°F. in the gastrocnemius, with 98 or 99°F. being the average temperature of the muscle. Furthermore, after the pack is removed and the bed clothes are replaced the muscle maintains this elevation and its increased circulation for some period. There is little drop during the first hour and only a small amount at the end of two hours. After three hours the temperature of the muscle approaches the temperature which existed prior to the application of heat.¹³ Barcroft and Edholm¹⁴ have correlated changes in muscle temperature with the blood flow in the forearm of normal subjects. They found that the flow is almost doubled when muscle temperatures are elevated from 89.6 to 95°F. This was a usual initial response. Furthermore, these observers have

brought forth good evidence that the increased blood flow occurs equally in muscle and skin under these conditions.¹⁵ It is known that the application of local heat does raise the temperature of the muscles and increases its blood flow. Whether these actions alone account for the greater part of the effect of the local heat is not certain. At any rate it is a fairly general observation that locally applied moist heat is helpful in relieving pain in poliomyelitis and its use in various forms preliminary to physical therapy seems to aid in developing ranges of motion and in correcting deforming attitudes. Watkins,¹⁶ however, using the total voltage of electrical potentials contributed by a particular muscle during a standardized stretching period as an index of spasm, concluded that a twenty-minute application of the Kenny type of hot pack was without significant effect as evaluated by this method. This technic, however, does not necessarily represent an evaluation of the clinical manifestation of spasm. Certain others¹⁷ observing a limited number of patients concluded that hot fomentations have no clearcut effect in aiding the return of normal ranges of motion. Heat does, however, seem to reduce the irritability and properly used has come to occupy a respected place in therapy.

METHODS OF APPLYING MOIST HEAT

Hot Packs. The first specific reference to hot packs with which we are familiar was made by Bradford, Lovett, Brackett, Thorndike, Soutter and Osgood¹⁸ in 1909. They stated that, "The application of heat, either as warm, moist or dry packs . . . will often be found to relieve pain." Subsequently, Legg¹⁹ and others included hot packs as an adjunct to relieve the sensitiveness and to facilitate the performance of muscle re-education and the maintenance of full joint mobility.

Numerous types of fomentations have been advocated. Many have placed great emphasis upon the details of their application and certain routines have been recom-

mended which involve frequent intensive packing for each patient and require extensive personnel. Two general types of packs are in current use: one may be called the "wrap-around pack" and the other the "lay-on pack." Since the recommendations of Kenny,²⁰ woolen cloth has come to be the favored material for use and it does have certain advantages. Both types of packs follow the general plan of application directly to the skin of the hot, wet wool from which the water has been well wrung. This pack is then covered by two additional layers, one of a waterproof material and the second of other material which is applied for additional insulation.

The Kenny pack is a wrap-around type of pack and its preparation and use has been described in detail elsewhere.²⁰ The materials used in the pack are of three shapes, square, rectangular and triangular, depending upon the part to be covered. The inner portion, composed of two layers of wool flannel, is taken directly from boiling water, is run through a wringer twice and immediately wrapped about the part smoothly and firmly. The pack is as hot as the patient can tolerate. Around this inner pack is wrapped a layer of waterproof material of similar shape, a single layer of dry flannel and finally an outer layer of cotton flannel or terry cloth which is pinned in position. Kenny recommends that essentially all parts of the body and extremities should be packed except the major joints which should not be covered in order that there be no restriction of motion. This entails many individual packs. In the acute stage the packs are described as being renewed every hour for twelve hours per day. During the convalescent stage they are renewed every two hours during the day until all signs of spasm and tightness have disappeared. This is mentioned as usually requiring six or eight weeks but may continue for many months. If the spasm is severe, and on special indications, the packs may be applied more frequently and at night.

Such application of packs makes a tremendous

demand upon personnel. In practice many modifications of this technic have evolved. These variables include methods of applying the packs, the frequency with which they are applied and the areas which are covered.

The lay-on type of pack is more simple and rapid in its application. As its name implies it is laid in position over the part. It is more frequently used with the patient in the prone position to cover the neck, back, shoulder girdle, buttocks, thighs and calves although this type may be used in any area. For the packing in a prone position usually one pack rectangular in shape is used to cover the trunk from the occiput to the gluteal fold, and two other rectangular packs are applied to each lower extremity extending from the buttocks to include the heel and foot. Usually they are applied only to those areas which are most sensitive.

Circumstances and the availability of equipment and materials often determine the type and method of applying hot fomentations. For specific details and means of improvising equipment the reader is referred to two summaries of nursing care for poliomyelitis patients.^{21,22} Commercial machines which deliver the packs heated and of the desired water content are available and simplify their application.

In our experience Munsingwear in four thicknesses has been found to be a very satisfactory and economical material for the inner portion of the pack. Koroseal has proven to be a serviceable water-proof material and a covering layer of wool cloth is used for additional insulation. The four thicknesses of Munsingwear constituting the inner layer are stitched together around their edges and diagonally. The Koroseal and outer wool covering are sewn together along their edges. Thus the application is simplified by having what amounts to two layers to apply rather than three or four.

Hot packs should be used for specific purposes. They may well be omitted in a patient with little sensitivity or spasm and they should be employed only in those areas



FIG. 1. "Lay-on" type of pack as used in the prone position. The hot inner pack is in place; the outer water-proof and insulating layer is about to be carried up over the trunk. Note that the pack is carefully tucked under and about parts.

in which sufficient sensitivity exists to indicate their use. In practice the lay-on packs are adequate for most patients. When patients are in a prone position, such packs can be applied to cover the greater part of the body with direct application to the areas which often are most sensitive. If the pack is carefully tucked around under the shoulders, trunk, hips and around the sides of the thigh and legs, a greater part of the surface is covered. In very sensitive patients the lay-on rather than the wrap-around pack is almost a necessity in order not to cause the patient more discomfort by the additional handling necessary to their application. (Fig. 1.)

In general, continuous packing is not recommended. It tends to be debilitating and we do not believe it has any particular advantage. If such packing is performed, adequate fluid intake and urinary output must be maintained. During the febrile

period additional sodium chloride should be given.

The technic which we usually follow is that of using the lay-on pack over a period of approximately thirty minutes. The packing is repeated once during this time. As a rule three or four packing periods of thirty minutes each, distributed at four- to six-hourly intervals during the day and evening suffice. Often only two or three packs are used and then only to areas where they are indicated. Night packs should be used if the patient is awake and uncomfortable but never should he be awakened for their application. Packs seldom need repetition within three hours. As Gucker has shown the temperature of the muscle is raised very definitely by a twenty-minute pack and this elevated temperature is maintained for two to three hours. Occasionally, more frequent selective packing of an area may be used if there is spasm

of the intercostal muscles and accompanying respiratory embarrassment. When the sensitivity is extensive, the wrap-around packs may be used in particular areas. If it is concluded that packs are indicated, the areas which are covered and the frequency with which the packs are employed should be geared to the individual patient. Observation of his subjective and objective reactions to the packs are of assistance in decisions regarding their use.

Hot packs have particular value preliminary to physiotherapeutic measures. The heat tends to relax tight structures and allows greater ranges of motion to be developed without provoking pain. As soon as the acute illness is over gentle passive motion to correct deforming tendencies and to increase range of motion should be employed after use of the packs. Ordinarily physical therapy should immediately follow the packs or at least it should be carried out within one hour after they are removed in order to take advantage of the increased relaxation and circulation. Preliminary heating, furthermore, seems to facilitate active exercises especially during the sensitive and early asensitive portions of the convalescent stage. It is our custom to provide physical therapy twice daily in addition to careful changing of positions by the nursing staff.

Some patients do not tolerate hot packs well and if they do not seem to be of value they should be discontinued. Particularly when they are first given, the packs should never be so hot as to cause discomfort. Occasionally the skin is irritated by the wool. Such patients generally tolerate heat given by immersion in a warm bath or tub, especially if the water temperature is raised gradually rather than being too hot at the start. No magical effect upon the disease process arises from the use of hot packs. Other measures are more important in the care of patients with poliomyelitis but moist heat is helpful in arriving at certain objectives.^{23,24}

Warm Baths. Heine²⁵ in 1840 first commented on the use of warm and steam baths



FIG. 2. The Hubbard tub. The patient is transferred to the tub without eliciting pain. The water is usually between 98 and 101°F. The warm bath relieves pain, allays muscle sensitivity and spasm and permits ranges of motion and other desired maneuvers to be accomplished more freely and with less discomfort.

in the treatment of poliomyelitis. Subsequently, Wickman,²⁶ Lovett,²⁷ Lowman^{28,29} and Legg³⁰ described the use of baths and underwater therapy for the disease's various stages. Since 1928 the tub developed by Mr. Carl Hubbard has been used extensively.³¹ This tub is particularly shaped to facilitate handling of the patients during their period of exercise. (Fig. 2.)

The warm bath is an excellent way to apply moist heat. It may be employed as soon as the acute illness is over providing that the facilities and technics for handling the patient are such that he can be placed in the tub without provoking pain or trauma. In many places use of the bath is deferred until two weeks after the onset, which is a common period for quarantine. The water should not be uncomfortably

hot and ordinarily should be somewhere between 98 and 101°F. Occasionally water of slightly higher temperatures up to 104°F. is not uncomfortable for certain individuals. The patient ordinarily should not be left in the tub for longer than twenty minutes in order to avoid enervating effects. A longer or a shorter time may be appropriate for the individual patient.

The warm bath soothes pain and sensitivity and relaxes the muscles. Exercises are performed while the patient is in the tub. The relaxing effect on the tight muscles allows a greater range of comfortable motion. The parts are gently carried out of deforming attitudes and ranges of motion can be developed more comfortably and easily. In addition, the buoyancy of the water and the warmth permit the weakened muscles to perform more effectively. In motion of large parts the therapist can more easily control the movements. Frequently the bath is employed once a day and hot packs are given to particular areas at other times. The bath is especially indicated in patients who have extensive involvement. It is not within the province of this discussion to consider the general field of underwater exercises.

SUMMARY

The value of the hot pack has been exaggerated by many. Use of moist heat is a helpful adjunct in therapy but many other features of treatment are more important. There is no evidence that extensive, continuous packing should be practiced in poliomyelitis. Moderate use of packs seems to be helpful. Local heat applied for twenty minutes does raise the temperature of subjacent muscles to a significant degree for a period of two to three hours. Hot packs and baths tend to relieve pain, assist in making patients more comfortable and promote relaxation of tight muscles. Their use is particularly valuable immediately preceding physiotherapeutic measures which are designed to correct deforming tendencies and increase ranges of motion. Moist heat of itself will not accomplish these objectives.

The hot bath, particularly as it can be given in the Hubbard tub, is to be commended.

REFERENCES

1. RANSON, S. W. and SAMS, C. F. A study of muscle in contracture; the permanent shortening of muscles caused by tenotomy and tetanus toxin. *J. Neurol. & Psychopath.*, 8: 304, 1928.
2. LOVETT, R. W. Infantile paralysis in Vermont 1894-1912. *J. A. M. A.*, 64: 2118, 1915.
3. KABAT, H. and KNAPP, M. E. The mechanism of muscle spasm in poliomyelitis. *J. Pediat.*, 24: 123, 1944.
4. BODIAN, D. Poliomyelitis, neuropathologic observations in relation to motor symptoms. *J. A. M. A.*, 134: 1148, 1947.
5. BARNHART, M., RHINES, R., McCARTER, J. C. and MAGOUN, H. W. The distribution of lesions of the brain stem in poliomyelitis. *Arch. Neurol. & Psychiat.*, 59: 368, 1948.
6. KATZ, L. N., LINDER, E. and LANDT, H. On the nature of the substance (s) producing pain in contracting skeletal muscle; its bearing on problems of angina pectoris and intermittent claudication. *J. Clin. Investigation*, 14: 807, 1935.
7. ELLIOTT, A. H. and EVANS, R. D. Ischemic pain in exercising muscle. *Am. Heart J.*, 12: 624, 1936.
8. SMITH, E., ROSENBLATT, P. and LIMAURO, A. B. The role of the sympathetic nervous system in acute poliomyelitis. *J. Pediat.*, 34: 1, 1949.
9. GUCKER, T., GREEN, W. T. and ANDERSON, M. A. Observations on the skin and muscle temperatures in poliomyelitis. To be published.
10. KRUSEN, F. H. Physical Medicine. Chap. 3. Philadelphia, 1941. W. B. Saunders Co.
11. BAZETT, H. C. The physiological basis for the use of heat. In Principles and Practice of Physical Therapy by Mock, Pemberton and Coulter. Chap. 4, Hagerstown, Md., 1932. W. F. Prior Co.
12. BIERMAN, W. Physical Medicine in General Practice. Chap. 1. New York, 1948. Paul W. Hoeber.
13. GUCKER, T. The effects of various forms of heat on skin and muscle temperatures of the extremities. To be published.
14. BARCROFT, H. and EDHOLM, O. G. Temperature and blood flow in the human forearm, *J. Physiol.*, 104: 366, 1946.
15. BARCROFT, H., BONNER, W. McK., EDHOLM, O. G. and EFFROM, A. S. On sympathetic vasoconstrictor tone in human skeletal muscle. *J. Physiol.*, 102: 21, 1943.
16. WATKINS, A. L. and BRAZIER, M. A. Observations on muscle spasm in poliomyelitis. *Arch. Phys. Med.*, 20: 325, 1945.
17. KOTKE, F. J., TEIGEN, B. S., SIEGEL, S. and KNAPP, M. E. Evaluation of aids to muscle reeducation in the treatment of poliomyelitis. *Arch. Phys. Med.*, 29: 141, 1948.
18. BRADFORD, E. H., LOVETT, R. W., BRACKETT, E. G. THORNDIKE, A., SOUTTER, R. and OSGOOD, R. B. Infantile paralysis in Massachusetts in 1909. III. Methods of treatment in infantile paralysis. *Bull. Massachusetts State Board Health*, June, 1910.
19. LEGG, A. T. The early treatment of poliomyelitis and

- the importance of physical therapy. *J. A. M. A.*, 107: 633, 1936.
20. POHL, J. H. and KENNY, ELIZABETH. The Kenny Concept of Infantile Paralysis and Its Treatment. Bruce, Minn., St. Paul, 1943.
21. A Guide for Nurses in the Nursing Care of Patients with Infantile Paralysis. New York, 1946. The National Foundation for Infantile Paralysis, Inc.
22. Nursing for the poliomyelitis patient. The Joint Orthopedic Nursing Advisory Service, New York, 1948.
23. GREEN, W. T. Methods in the treatment of anterior poliomyelitis. *Post-Grad. Med.*, 1: 352, 1947.
24. GREEN, W. T. Present-day status of poliomyelitis. *New England J. Med.*, 238: 73, 1948.
25. HEINE, J. Beobachtungen ueber Laehmungszustände der unteren Extremitäten und deren Behandlung. Koehler. Stuttgart, 1840.
26. WICKMAN, O. Acute poliomyelitis (Heine-Medin's disease). *Nerv. & Mental Disease Monograph*, Series No. 16. New York, 1913.
27. LOVETT, R. W. A plan of treatment in infantile paralysis. *J. A. M. A.*, 67: 421, 1916.
28. LOWMAN, C. L. The underwater gymnasium as an adjunct to orthopaedic surgery. *J. Bone & Joint Surg.*, 9: 119, 1927.
29. LOWMAN, C. L. The technique of water gymnastics in muscular reeducation. *Am. Phys. Rev.*, 1, 1928.
30. LEGG, A. T. Physical therapy in infantile paralysis. Principles and Practice of Physical Therapy. Vol. 2. Hagerstown, Md., 1932. W. F. Prior Co.
31. BLOUNT, W. P. and ELSON, M. A new hydrotherapy tub. *J. Bone & Joint Surg.*, 10: 506, 1928.

Bulbar Poliomyelitis*

Its Mechanism and Treatment

A. B. BAKER, M.D.

Minneapolis, Minnesota

IN spite of extensive studies on poliomyelitis, particularly during the past few years, very few publications have been devoted exclusively to the subject of the bulbar involvement in this disease. It is this latter form of the illness, however, that produces most of the fatalities and normally should warrant the attention and energetic investigation of the profession. For years there seems to have developed a fatalistic attitude regarding bulbar poliomyelitis—an attitude that is an admission of lack of understanding of the underlying mechanisms producing the various clinical manifestations and inability to cope with them. Recent advances in the fields of neuroanatomy, neuropathology and neurophysiology make it both possible and advisable to re-examine the problem of the cause of death in bulbar poliomyelitis in the light of this new knowledge, with further efforts being directed at more intelligently combating this disease.

One of the chief difficulties in studying this illness in detail has been the infrequency with which a large number of critically ill patients have been available to the same investigator within a relatively short period of time. During the 1946 epidemic in Minnesota such an opportunity became available to us. Within a four-month period 183 cases of bulbar poliomyelitis were admitted to the University Hospital alone. This large number of cases afforded us an opportunity of viewing this illness in all its clinical manifestations. It also offered an opportunity to study the effectiveness of various therapies and to investigate the pathologic physiology of this disease.

Generally, bulbar poliomyelitis has been considered clinically as a single disease entity in spite of a most diverse and widespread symptomatology. This attitude has retarded our progress and understanding of this illness. From our studies it is apparent that adequately to understand and treat this illness, it must be broken down into different groups, each with a predominant pathology and symptomatology. It must be emphasized that the various groups do merge into each other and rarely occur in pure form; however, such a classification does make for a more rational and intelligent approach to this illness.

GROUP I: CRANIAL NERVE INVOLVEMENT

In this group both the clinical symptoms and the pathologic lesions are limited to the nuclei of the cranial nerves. The brainstem reveals a mild inflammatory reaction consisting of both diffuse and perivascular mononuclears intermixed with numerous polymorphonuclears. The nerve cells show a patchy swelling and chromatolysis. The degree of neuronal damage is most variable from case to case, in some being very mild while in others destroying complete cell groups.

The clinical manifestations are generally correlated with the cranial nerve damage. Isolated ocular palsies such as ptosis and squints, total external ophthalmoplegias as well as pupillary disturbances may occur due to partial or complete involvement of the third nerve nuclei. Such ocular manifestations were not common in the patients at the University Hospital; they occurred in but 11 per cent. Disturbances of mastication

* From the Division of Neurology, University of Minnesota Medical School, Minneapolis, Minn. Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

tion result from damage to the motor division of the fifth cranial nerve. Such palsies may be unilateral or bilateral and may implicate part or all of the muscles supplied by the fifth nerve. In unilateral lesions the jaw may deviate spontaneously when the patient opens his mouth, while at times the action of the pterygoid muscles must be tested by sideward deviation of the jaw against resistance. In isolated cases the patient may develop an acute severe trismus due to irritation of the fifth nerve nucleus. This may be a serious complication since inability to open the mouth prevents adequate removal of the secretions and may result in obstruction of the airway. We have observed this unusual complication in three patients. In such cases immediate tracheotomy is often necessary to prevent airway obstruction by secretions.

Paralysis or paresis of the facial nerve is observed fairly frequently in bulbar poliomyelitis and occurred in 53 per cent of our patients. In some cases the whole distribution of the facial nerve is involved; in others only one branch may be involved, such as that which supplies the cheek, the forehead or the lips; finally in still others the involvement is patchy, implicating one group of facial muscles on one side of the face and another set on the opposite side.

Bilateral deafness and vestibular disturbances may occur. Nystagmus was observed in several of our patients.

Involvement of these upper cranial nerve nuclei generally holds no threat to the life of the patient may be annoying and may result in residuals which can produce definite handicaps. They are of importance nevertheless because they should make the physician alert to the possibility of implication of more vital centers.

By far the most frequent cranial nerve involved in bulbar poliomyelitis is the tenth. These patients develop a weakness or paralysis of the soft palate, the pharynx and vocal cords. Their initial complaint often is a nasal twang to the voice, hoarseness, increased accumulation of secretions in the oropharynx or difficulty in swallow-

ing. On examination there is generally pooling of saliva in the throat, the patient being unable to handle his secretions by swallowing. The speech has a nasal quality and may be hoarse from faulty innervation of the vocal cords. An occasional patient is unable to talk. Laryngeal stridor may be present. Weakness of the tongue may be bilateral or unilateral and may impair movement of food through the mouth and impede expectoration of saliva.

Considerable importance must be placed on lesions of the tenth cranial nerve because this nerve in conjunction with the eleventh and twelfth is essential for consummation of the act of swallowing. With inability to swallow there is the constant tendency toward pooling of saliva and food in the pharynx. This accumulation produces obstruction to the airway. A further threat to the airway results from the aspiration of fluid into the larynx or from reflex spasm of the glottis.

Interference with the airway should be combated by postural drainage and/or suction. However, in our experience it frequently has proved impossible to maintain an open airway by such measures even when constant suction is applied. When such procedures fail, tracheotomy should be resorted to immediately. Maintaining an unobstructed airway is of extreme importance in the care of these patients since any period of hypoxia, whether acute or chronic, can do irreparable damage to nerve cells already injured by the inflammatory process. Early evidence of such hypoxia generally consists of restlessness, apprehension, sleeplessness and increasing pulse rate and respiratory effort. The appearance of these latter symptoms in patients with lower cranial nerve involvement should immediately stimulate one to investigate those factors that might produce obstruction: (1) pooling of secretions due to paretic throat muscles; (2) paralysis of the tongue; (3) obstructed airway due to reflex spasm of laryngeal musculature; (4) obstructed airway due to abductor paralysis of the vocal cords; (5) accumulation of secretions

due to inability to cough; (6) aspiration of vomitus.

The appearance of laryngeal stridor, dyspnea (despite adequate chest excursion), cyanosis and severe encephalitic symptoms indicates that the obstruction to the airway has not been remedied and that severe hypoxia has now developed. Such symptoms warrant emergency measures to clear the airway. It must be remembered that in patients with partial or complete obstruction of the airway there are strong inspiratory efforts in an attempt to overcome hypoxia. These inspiratory efforts in the face of an obstruction produce a relatively high negative pressure in the bronchioles and alveoli. This negative pressure sucks fluid, plasma and even red cells out of the pulmonary capillaries into the alveoli, producing acute pulmonary edema and death.

If the airway cannot be maintained unobstructed by postural drainage and/or suction, one may have to resort to tracheotomy in selected cases. After tracheotomy patients with bulbar poliomyelitis still require constant care and supervision. It is necessary to continue to aspirate the accumulation of fluids in the pharynx, particularly during the first few days following the tracheotomy. The tracheal cannula must be inspected and cleared frequently. Generally, the tracheal secretions become very viscid and unless the inspired air is adequately humidified, they are very difficult to remove. In order to humidify the inspired air and at the same time deliver a measured amount of moistened air and oxygen mixture directly through the tracheotomy tube, an apparatus called the tracheotomy inhalator has been used by us.¹ This inhalator is so constructed that expiratory and inspiratory pressure can be controlled independently as the emergency demands. This inhalator has the added advantage of permitting the delivery of oxygen mixtures of various percentage concentrations under optimal pounds of pressure. Patients are generally given about 50 per cent oxygen concentration in the inhalation mixture. In all cases

oximetry should be employed in order to determine the effectiveness of oxygen therapy. The oximeter is an instrument which determines the relative concentration of oxyhemoglobin to reduced hemoglobin by means of a photo-electric cell. This instrument is of great aid in establishing the efficiency of measures taken to promote adequate oxygenation of the patient in the presence of hypoxia or impending hypoxia.

In spite of tracheotomy and apparent adequate drainage, it has been found advisable to rotate the patient constantly in order to avoid pulmonary hypostasis. This procedure proves most satisfactory providing the patient is rotated at least 30 degrees or more every hour. If the patient is not in a respirator, the rotation should be more complete, extending to the maximum of 90 degrees. Such a procedure has enabled us to keep the lungs clear in many patients in whom pulmonary edema was already developing and has greatly reduced the incidence of our pulmonary complications.

In 100 patients with bulbar symptoms limited to the cranial nerves there were five deaths, four of which occurred before an adequate airway could be secured.

GROUP II: RESPIRATORY CENTER INVOLVEMENT

Many individuals with bulbar poliomyelitis have symptoms and findings indicating involvement of the respiratory center in the medulla in addition to varying degrees of pareses of the cranial nerves. Pathologically, they show in the medulla at the level of the inferior olive, a most extensive bilateral focal necrosis involving the lateral ventral reticular substance. In most cases these lesions consist of areas of inflammatory necrosis, with a fragmentation of the underlying tissues. These inflammatory areas could well be produced by the virus of poliomyelitis. On the other hand, certain of the necrotic areas are filled with fat granule cells and show no evidence of an actual inflammatory process. It is suspected that the etiology of these

latter lesions may well be due to a secondary hypoxia resulting from the respiratory difficulties. Generally the cranial nerve nuclei in the involved areas reveal only minimal changes. Even the nucleus ambiguus, which is situated adjacent to these areas of inflammatory necrosis, is surprisingly free of alterations.

Clinically, the outstanding symptoms are respiratory and correlate with the involvement of the respiratory center in the medulla. During the course of illness irregularities of rhythm and depth of respiration develop. These respiratory symptoms appear in the face of an adequate airway and intact respiratory musculature. The respirations tend to be shallow and there are often prolonged intervals between inspirations. At this point the patients generally show some degree of anxiety, restlessness, increase in pulse rate and some elevation of blood pressure. These symptoms indicate an early hypoxia even though there may be no clinical cyanosis. Such impending failure of the central respiratory mechanism makes it imperative that oxygen therapy be instituted. If oxygen therapy has already been started it is advisable to increase the concentration of oxygen being administered. The effectiveness of the oxygenation can generally be followed by the use of the oximeter and checked by determinations of the arterial oxygen.

As failure of the respiratory center in the medulla progresses, there are increasing periods of apnea with beginning Cheyne-Stokes respiration. The temperature and pulse rate tend upward and the blood pressure may be elevated or may fall to shock levels. Confusion, delirium and coma soon appear. The periods of apnea become more prolonged until finally respirations cease. These latter symptoms require immediate intensification of oxygen therapy; however, the concentration of oxygen used should ordinarily not exceed 60 per cent. In emergencies it may be increased to 100 per cent for a limited period of time. Sedation of any sort should be avoided in this group of patients or should be used

with extreme caution because of the depressant effect on an already damaged respiratory center.

GROUP III: VASOMOTOR INVOLVEMENT

A few patients will show severe circulatory collapse with minimal or no cranial nerve palsy and no respiratory involvement. In such cases one is often forced to make a diagnosis of bulbar poliomyelitis in spite of apparently normal function of the cranial nerves. It is this type of involvement that may frequently be overlooked and the diagnosis not made. When the symptoms of bulbar poliomyelitis indicate circulatory involvement, the prognosis generally is extremely grave. The clinical features in this type of bulbar poliomyelitis are very characteristic. These patients have a dusky red, flushed, florid appearance. The lips are deep cherry red. The pulse is extremely rapid, ranging between 150 and 200. It is often irregular and at times difficult to palpate. The blood pressure varies from elevated to low levels, and the pulse pressure may be as low as 10 mm. of mercury. In children the blood pressure has a greater tendency to become elevated. Very early in the illness these patients show marked restlessness, apprehension and anxiety, indicating early onset of a mild or moderately advanced hypoxia. The course in this illness is very rapidly downhill; the skin soon becomes cold, clammy and has a mottled cyanosis. The temperature begins to rise and at the same time the respirations tend to become shallow. Terminally, these patients become markedly confused, finally comatose and the heart beat is inaudible before respirations cease.

At necropsy the lungs seem to be the site of severe hemorrhagic pulmonary edema. Sections through the medulla reveal areas of bilateral focal necrosis which are situated in the medial ventral reticular substance. In most cases one can detect mild inflammatory lesions in the medulla and many of the cranial nerve nuclei show a scattered involvement. These histologic lesions seem very significant in view of the experimental

work of Wang and Ranson² who were able to stimulate the brainstem and study the effect upon blood pressure in cats by using the Horsley-Clarke stereotactic instrument. It was apparent from their work that there was a pressor response when the dorsal reticular substance of the medulla just beneath the floor of the fourth ventricle was stimulated. Depressor responses were more diffuse and seemed to be localized primarily in the ventral medial reticular substance of the medulla oblongata. It is in this latter region that we observed pathologic lesions in cases of bulbar poliomyelitis manifesting circulatory symptoms. It would appear, therefore, that when the inflammatory process in poliomyelitis involves the medial ventral reticular substance of the medulla it destroys the vasomotor center and produces marked circulatory responses.

The treatment of the circulatory type of bulbar poliomyelitis is very unsatisfactory at the present time. These patients tend to develop a very rapid pulmonary edema, very severe hypoxia and terminate fatally in a few days. The mortality rate in our cases was 83 per cent. It is believed at the present time that the best treatment consists of intensive oxygen therapy and maintenance of a clear, unobstructed airway at all times. Such oxygen therapy is used to combat the hypoxia and thus prevent the addition of hypoxic damage to centers already injured by the virus invasion. Supportive measures in combating the shock may be used but these seem to be of only temporary benefit.

GROUP IV: SPINOBULBAR INVOLVEMENT

In this group are included those cases in which there is combined involvement of both the medulla and the cervical and thoracic cord. These patients, therefore, in addition to the bulbar symptoms require treatment in the respirator because of the severe damage to the upper part of the spinal cord, resulting in failure of the diaphragm and the intercostal muscles.

This combined involvement is discussed in a separate group because it results in specific therapeutic problems which are not encountered in isolated involvement of either the spinal cord or the medulla. The symptomatology in these patients, in addition to the paralysis of the diaphragm and intercostal muscles, will depend upon the region of the medulla involved and will manifest itself either in cranial nerve palsies or as cardiorespiratory disturbances. Because of the involvement of the diaphragm and intercostal muscles it becomes necessary to place these individuals in the respirator. Whenever a patient with bulbar poliomyelitis is placed in a respirator, it becomes imperative to insure an open airway. It must be kept in mind that inspiration forced by the respirator against a partially obstructed airway will create a relatively marked negative pressure in the alveoli, sucking fluid out of the pulmonary capillaries and producing a very acute pulmonary edema. These patients, therefore, must be watched constantly over the twenty-four-hour period to be sure that obstruction does not result. They should be suctioned constantly; and if it appears that the airway cannot be kept open by suction and/or postural drainage, tracheotomy must be considered. In order to use tracheotomy in respirator patients it is necessary to have available a respirator with the front modified so that the respirator head is tilted forward about 6 inches allowing for accessibility to the patient's neck as far as the sternal notch. This modified form of respirator head is now available and can be obtained for the standard makes of respirator. The oximeter is of great value in these patients for indicating the efficiency of the therapeutic measures and determining how long a patient can be left out of the respirator. The appearance of restlessness, apprehension, anxiety, increasing pulse rate and fever indicates an incipient hypoxia, even in the absence of cyanosis, and should alert one to check the patient carefully for possible obstruction to the airway.

In all cases of bulbar poliomyelitis the use of drugs generally is largely prophylactic

and supportive. Since there is a high percentage of pulmonary complications in this disease, intramuscular injections of penicillin are often useful as a prophylactic. In addition, penicillin may be nebulized into the tracheotomy tube at regular intervals if tracheotomy has been performed. When mild anemia develops during the course of the illness, a transfusion of whole blood or plasma is often indicated. Excessive intravenous administration of fluids should be avoided whenever possible, primarily because of the danger of pulmonary edema. Sedatives of any sort should be avoided because of the danger of further impairing bulbar function in an area which is already functioning at a very poor level.

In most cases of bulbar poliomyelitis nutrition is of the utmost importance. During the first few days, particularly if the patient is unable to swallow, it is advisable to use fluids parenterally. Giving any fluids or food by mouth in a patient who is having difficulty in swallowing is extremely dangerous because of the possibility of regurgitation and obstruction of the airway. After the acute stage of the illness has subsided the patient may be fed by nasal tube. In such cases the feedings should be given in very small amounts and sufficient time allowed for absorption. One must always be on the alert for the possibility of regurgitation of such nasal feedings with aspiration of the formula. Not infrequently in bulbar poliomyelitis, the patient develops a complete parasympathetic involvement of the gastrointestinal tract. They have an extremely atonic stomach which will not propel the food into the intestinal tract. This allows the food to accumulate in the stomach and encourages regurgitation and secondary aspiration. Such patients must always be fed very small amounts. This condition can also be improved by the daily injections of prostigmine, 0.5 mg. every two hours. The ability of these patients to swallow should be tested from time to time, beginning with fluids and progressing to soft, and then finally to solid food. When swallowing is fairly well established, the

nasal tube can be removed; and if tracheotomy has been instituted, the tracheotomy tube can be stoppered and later removed.

CONCLUSIONS AND SUMMARY

1. Bulbar poliomyelitis, both clinically and pathologically, is not a single entity but can be divided into different groups, depending upon the region of the medulla involved by the pathologic process and the subsequent symptomatology.

2. By far the most frequent type of involvement is that of the cranial nerve nuclei. When the tenth cranial nerve is implicated, difficulty in swallowing and talking develops, with subsequent obstruction of the airway and asphyxia. These symptoms can be prevented by constantly keeping the airway open by means of suction, postural drainage and, when absolutely necessary, tracheotomy.

3. Some cases of bulbar poliomyelitis may implicate the autonomic centers of the medulla; namely, the respiratory and the circulatory centers. In these cases the symptomatology consists of either respiratory or circulatory failure even in the absence of severe cranial nerve involvement. The prognosis in such cases is somewhat doubtful since involvement of the autonomic centers results in very rapid development of hypoxia. The treatment of choice at the present time is intensification of oxygen therapy either by mask, internasal oxygen or by tracheotomy, when indicated.

4. When both the upper spinal cord and bulb are involved, the patient generally must be placed in a respirator. In such cases one must be constantly alert to maintain an open airway in order to prevent rapid pulmonary edema due to the forced inspiration resulting from the use of the respirator.

REFERENCES

1. KUBICEK, W. G., HOLT, G. W., ELAM, J. O., BROWN, J. R. and GULLICKSON, G. Oxygen therapy in poliomyelitis. *Arch. Phys. Med.*, 29: 217-225, 1948.
2. WANG, S. C. and RANSON, S. W. Autonomic responses to electrical stimulation of the lower brain stem. *J. Comp. Neurol.*, 71: 437, 1939.

Care of the After Effects of Poliomyelitis*

ROBERT L. BENNETT, M.D.

Warm Springs, Georgia

THE obvious purpose of the treatment of the after effects of acute anterior poliomyelitis is to assist the patient to develop the highest possible degree of functional capacity within the unalterable limits defined by the lesion in the central nervous system. Less obvious may be the realization that to achieve this goal our program of care must be based on the philosophy that the end result will depend not only on the damage to the central nervous system but on what is done with what is left anatomically intact and thus potentially available for use. Least obvious is the understanding that the most detailed and exact treatment will fall far short of achieving maximum functional results if all of the factors that determine these end results are not fully understood.

There are four basic factors that determine the end result:

1. *The Site and Extent of Central Nervous System Damage.* This factor is of importance not only because it limits the number of neuromuscular units available for use but also because certain deformities of the skeletal system must follow certain patterns of damage in the nervous system. For example, if a large portion of the nerves that innervate the skeletal muscles of a bodily segment, such as the leg and foot, are destroyed, normal strength and endurance of those muscles can never be obtained regardless of treatment. In a child, serious alteration of osseous structure and growth may also occur despite the best of care.

2. *The General Medical Condition of the Patient during the First Few Months after the Acute Illness.* Many patients are so severely involved that their general medical condition prohibits application of convalescent

routes that under more favorable circumstances would limit the development of musculoskeletal deformities and faulty patterns of motion. For example, the patient who must be kept in a respirator cannot be cared for adequately and will develop changes in bone, muscle, fascia, joint and peri-articular structures that will be, in great part, irreversible regardless of the highest type of available treatment.

3. *The Caliber of Available Care.* The average patient with residual weakness following poliomyelitis is at best a difficult problem in rehabilitation, requiring for optimal end results the combined skills and experiences of the internist or pediatrician, the physiatrist and the orthopedist. Many patients with only minimal involvement who could be expected to recover normal functional capacity with intelligent care develop severe handicaps because of early weight bearing, unrestricted activity and failure of the attending physician to recognize mild muscle imbalance and incipient deformity. It must be stressed that the patient, child or adult, regardless of how mild the residual involvement may seem, must be repeatedly checked to determine the effect of increasing growth, weight and activity on skeletal structures. The tragedies of progressive deformity, such as scoliosis, can be minimized only if responsible periodic examinations of the musculoskeletal system are made for many years after the acute episode.

4. *The Responsibility and Intelligence of the Patient and/or His Parents.* This factor could be included in the third category but it is of such importance that it deserves special attention. For all practical purposes the general personality of the patient and his

* From the Georgia Warm Springs Foundation, Warm Springs, Ga.

parents is second only to the skill of the physician in assuring the maximum recovery of functional capacity within the limits set by the pathology of the acute disease. It is, of course, impossible to provide hospital bed space for all patients throughout the entire period of their convalescence, but even if it were it would be inadvisable to do so. Prolonged hospitalization is to be avoided because of the danger of mental stagnation and loss of initiative and self-confidence. Return to normal environment and contact with physically normal people are all-important in the overall rehabilitation program. Under ideal conditions the patient should be hospitalized only until the period of rapid recovery has taken place and the correct patterns of movement consistent with the underlying disease have been established. From then on the long-term program to increase strength and endurance by graduated activity can best be carried out at home. In some instances only modified activity is necessary but in most a very definite routine of joint mobilization and graduated exercises must be carried out for many months or even years.

While a program of care must be based on a thorough understanding of the aforementioned factors that determine the possibilities of recovery, the success of the program will depend on the ability of the medical team to achieve four objectives: (1) Effective utilization of all intact neuromuscular units. (2) Prevention or minimizing of all musculoskeletal deformities that would limit the most effective use of these units. (3) Training of patient and parents in their responsibilities within the program. (4) Intelligent acceptance by the patient and his family of his ultimate physical limitations.

More specifically, a program to achieve these objectives must progress through seven distinct steps that may be outlined in the manner illustrated in the accompanying diagram.

The first step may at first thought be considered unnecessary in a convalescent program but is included to emphasize that

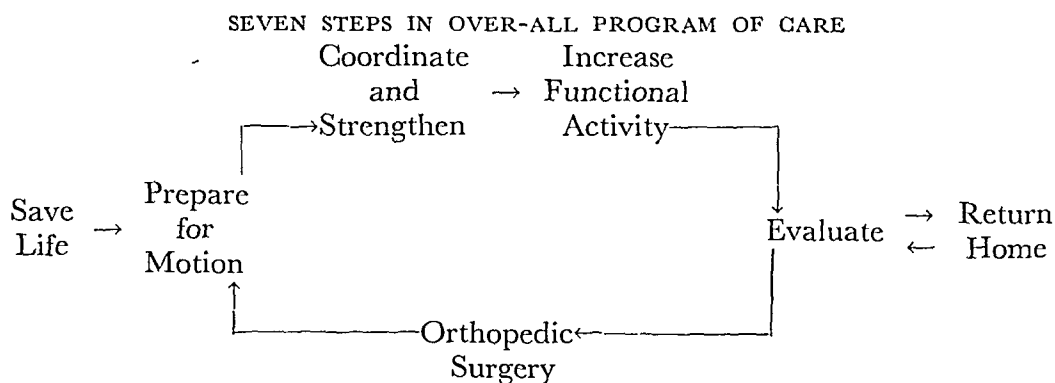
certain convalescent routines may actually endanger the patient's life if initiated too early in the acute or subacute phase or at any phase if carried out without regard for the patient's general medical condition.

The second step in our treatment program is the attempt to prepare the patient for resumption of activity. In a great majority of cases this will mean, first, preparation for long and tedious weeks of muscle re-education. It is at this point that a program of convalescent care really begins. The three major points in the preparation of any patient for resumption of activity are: (1) relief of pain; (2) release of any tightness in the muscles and joints; (3) support any bodily segment that is weakened.

It should readily be appreciated that coördinated action of muscle groups acting on any bodily segment is impossible if motion of that segment is limited by pain or by limitation of joint motion. Until this is done we can never fully regain the maximum use of existing myoneural units in any bodily segment. Relief of pain and the release of tightness are accomplished by time plus the use of intelligently prescribed sedatives, heat and passive motion. As in the use of all therapeutic agents the type and frequency of application of heat and motion depend on the reaction of the patient. There is no magical formula to achieve this end by any phase of physical medicine except through the intelligence and responsibility of the attending medical personnel. It is equally important in this step that we begin our endeavor to prevent musculoskeletal deformities. Deformities, except for atrophy and weakness following actual denervation, have just one cause: persistent faulty alinement of bodily segments which results in distortion of bones and joints and fibrous contractures of muscular and ligamentous tissue. In this early convalescent stage of poliomyelitis such malalinement results from persistent faulty posture in bed caused by such factors as pain, muscle weakness, faulty beds or the weight of bed clothes on weakened ex-

tremities. Therefore, it is of importance not only to preserve normal bodily mechanics and alinement by the early restoration of mobility in muscle and joint as just mentioned but also to prevent this persistent faulty posture by the most effective method

been restored. It is a continued source of amazement and gratification to see the extent of functional capacity that can be developed by patients with very little muscle power but highly developed coördination. It must be stressed that co-



possible. An effective support is not only one which holds the segments in proper position but also one which in no way interferes with the other components of early care. It should be quite evident that the type of support will depend on the quality of available medical supervision. Assuming adequate medical supervision is not available, a bivalved plaster cast may be more effective than pillows or sand bags. Under intelligent supervision an orthopedic bed, foot board, properly placed pillows and possibly a light plastic wrist and thumb splint are all the actual equipment needed to prevent deformities at this time.

The third step is to coördinate and strengthen the existing neuromuscular units. Certainly this step is the most important and probably the most difficult one in the entire program. It is in this step that we have made our greatest strides in the treatment of poliomyelitis during the past ten years—not because any outstanding discoveries have been made in functional anatomy or bodily mechanics but primarily because physical medicine has been given an opportunity to use its skill on bodily segments properly prepared for muscle re-education. It is obvious that the success of this step is absolutely dependent on the thoroughness with which the painless and complete mobility of the segment has

coördination and power are not the same. Power without coördination may be disastrous to the patient recovering from poliomyelitis because experience has taught us that all muscles in the involved segments do not recover with the same speed. If, as each of these individual muscles come under voluntary control, no attempt is made to coördinate their use, faulty habit patterns of motion will be built up by the patient with the use of these stronger and more easily available groups to the total exclusion of the weaker and thus less available groups. The development of a truly high degree of coördination in the patient with moderate to severe involvement demands the attention of a highly skilled physical therapist. No athlete ever needed a coach as badly as these patients need a physical therapist.

It is of the greatest importance to recognize that during this phase of our program all of our routines are based on the hope that sufficient return of muscular strength will occur to permit normal activity in a perfectly normal manner. It is for this reason that normal patterns of movement are stressed until adequate treatment given over a reasonable length of time has revealed the extent of damage to the nervous system and the limits of recovery possible.

How long should we persist in our en-

deavor to build up the strength of individual muscles by this intensive muscle re-education? The answer can best be summarized in Figure 1.

Experience has taught us that the recovery of strength in individual muscles or muscle groups follows a fairly definite curve or pattern. The end of the third month following the acute onset of weakness, a muscle receiving adequate and intelligent treatment has recovered approximately 60 per cent of the total strength that it will ever recover if treated for an indefinite period of time. During the second three months an additional 20 per cent returns for a total of 80 per cent return at the end of the first six months of adequate treatment. After this the recovery rate becomes increasingly slower so that by the end of eighteen months of treatment it can be reasonably assured that no further increase in individual muscle strength can be expected. By applying this recovery rate curve to specific cases it will be seen that a muscle rating of "poor minus" (10 per cent of normal) at the end of a six-month period of treatment can be expected to gain only an additional 20 per cent of that rating or a total of 12 per cent strength even if treated for a year longer. Obviously 12 per cent of normal strength would mean little or nothing in actual functional value and there would be no justification in treating such a muscle beyond the initial six months time. On the other hand, if a muscle rated "fair plus," or 60 per cent of normal, at the end of the first six months, the possibility of ultimately gaining an additional 20 per cent of that rating (72 per cent of normal) would be well worth working for, particularly if this muscle was one of the important weight-bearing groups.

During this phase the single muscle or muscle group is the unit of treatment. Obviously an accurate grading of these units in the involved segments is essential to the success of muscle re-education. No muscle test is adequate unless individual muscles and not movements are tested. At the Georgia Warm Springs Foundation

detailed test sheets are employed to record the strength of these individual muscles. Test sheets that mix muscles and movements brought about by many muscles are to be condemned.

Apparatus may be necessary to assist the

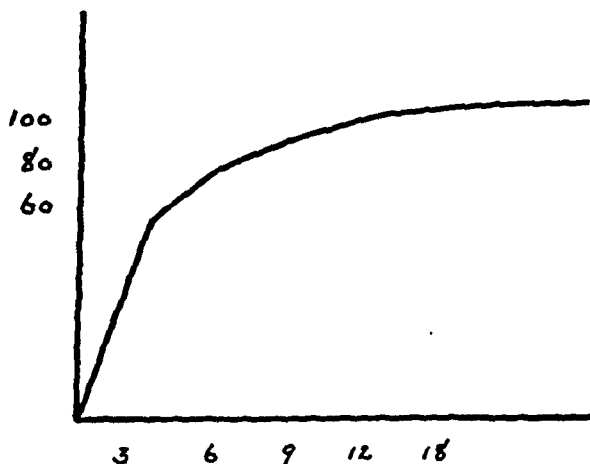


FIG. 1. The usual rate of recovery of individual muscle or muscle group strength under an adequate program of care. Abscissa, time in months; ordinate, per cent recovery.

normal actions of muscles at this time and should be considered a part of the treatment not an admission of defeat. They are applied to allow a more complete return of strength in the full hope that as strength returns they may be discarded.

The fourth step is increasing the actual functional activity of the patient. By the time this step is reached we should be able to determine with a fair degree of accuracy the extent of further improvement that is possible in the individual patient. Certainly, it will be known by then whether a patient will be able to return to a normal environment and carry on normal activities with normal patterns of motion. It will also be fairly obvious at this time whether it will be necessary to add some type of supportive or assistive apparatus to maintain this activity when the patient returns home. It is during this step that specific functional tests are given the patients to determine their ability to carry out certain activities that are required of them in a normal environment. When existing muscle strength and coördination permits, all of these activities are carried out in a normal man-

MUSCLE TEST SHEET, GEORGIA WARM SPRINGS FOUNDATION									
No.	Name		Date of Birth		Age		Diagnosis		
	Cannot Walk	Walks Unaided	With Braces	Left	Right	Crutches	Canes	Corset	Weight
Date									
Date									
Date									
Date									
Characteristic Gait									
Date									
Date									
Left	Trunk and Legs		Right	Left	Trunk and Legs		Right		
	S.C.M.			Middle	"		Middle		
	Neck			Lower	"		Lower		
Anterior			Anterior		Serratus magnus				
Lateral	"		Lateral		Rhomboids				
Posterior	"		Posterior		Latissimus dorsi				
	Respiration			Clavicular	Pectoralis major		Clavicular		
Upper	Back		Upper	Sternal	"		Sternal		
Middle	"		Middle		Outward rotators				
Lower	"		Lower		Inward rotators				
	Quadratus lumborum				Biceps				
Upper	Anterior abdominals		Upper		Brachioradialis				
Middle	"		Middle		Triceps				
Lower	"		Lower		Supinator brevis				
Ex. oblique			Ex. oblique		Pronators				
Internal oblique	Internal oblique			Ulnar	Wrist flexors		Ulnar		
	Transversalis			Palmaris longus	"		Palmaris longus		
	Gluteus maximus			Radial	"		Radial		
	Ilio psoas			Ulnar	Wrist extensors		Ulnar		
	Sartorius			Radial	"		Radial		
	Tensor fasciae latae			1 Profundus	Finger flexors		Profundus 1		
	Hip abductors			2	"		2		
	Hip adductors			3	"		3		
	Inward rotators			4	"		4		
	Outward rotators			1 Sublimis	"		Sublimis 1		
	Quadriceps			2	"		2		
Inner	Hamstrings		Inner	3	"		3		
Outer	"		Outer	4	"		4		
	Gastrocnemius			1	Finger extensors		1		
	Anterior tibial			2	"		2		
	Posterior tibial			3	"		3		
	Peroneals			4	"		4		
	Extensor longus digitorum			1	Lumbricales		1		
	Extensor brevis digitorum			2	"		2		
	Extensor proprius hallucis			3	"		3		
	Flexor longus digitorum			4	"		4		
	Flexor brevis digitorum			1	Dorsal interossei		1		
	Flexor lumbricales			2	"		2		
	Flexor longus hallucis			3	"		3		
	Flexor brevis hallucis			4	"		4		
	Measurements				Abductor minimi digiti				
Inspiration	Chest		Inspiration	1	Palmar interossei		1		
Expiration	"		Expiration	2	"		2		
	Calf			3	"		3		
	Thigh				Abductor longus pollicis				
	Length				Abductor brevis pollicis				
Contractures and Deformities					Adductor pollicis				
	Hip				Flexor longus pollicis				
	Knee				Flexor brevis pollicis				
	Ankle				Opponens pollicis				
	Scoliosis				Extensor longus pollicis				
					Extensor brevis pollicis				
					Contractures and Deformities				
					Shoulder				
Anterior	Deltoid		Anterior		Elbow				
Middle	"		Middle		Wrist				
Posterior	"		Posterior		Fingers				
Upper	Trapezius		Upper						

ner. If it is obvious that the damage to the motor system of the central nervous system is such that normal patterns of motion can never be achieved, the patient is given the necessary apparatus to support the activity and taught the most effective ways of using

crutch or corset whatsoever. Another patient might be able to achieve the same activity but only by using a long leg walking brace. Another patient, however, might have such severe involvement that walking will never be safe or practical, and

FUNCTIONAL TEST SHEET

Georgia Warm Springs Foundation

Functional Evaluation

Name: _____ Age: _____ Onset: _____
Occupation: _____ No. _____
Apparatus: _____

Grades Indicating Independence

- N Normal performance—patient apparently uninvolved.
- G+ Excellent performance—involvement apparent but speed, safety, endurance, and agility in performance no problem.
- G Adequate performance for all practical purposes.
- G- Adequate performance in a specific environment—limited to special types, styles, weights, heights, etc.

Grades Below Independence

- F Performance possible but not practical (speed, safety, etc.).
- P Performance is partial only (Example: Can get into chair but not out of it.)
- ? At this stage of treatment patient not allowed to perform the activity.
- X Activity not indicated for testing.
- O Activity impossible.

- 9 Bed (%)
- Operate signal light
- Hold letter
- Hold book
- Turn pages
- Write name
- Operate bed lamp and radio
- Procure object from night table
- Sit up
- Turn over
- 6 Eating (%)
- Eat with fingers
- Eat with fork
- Eat with spoon
- Drink from glass
- Drink from cup
- Cut with knife and fork
- 13 Hygiene (%)
- Use handkerchief
- Wash hands
- Wash face
- Brush teeth
- Comb hair
- Clean nails
- Trim nails
- Shave or make up
- Get on and off toilet
- Use toilet paper
- Bathe self
- Get in and out of bath or shower
- Shampoo hair
- 7 Dressing (%)
- Put on—remove underclothes
- Put on—remove buttoned shirt
- Put on—remove slipover garment
- Put on—remove slacks
- Put on—remove shoes
- Put on—remove hose
- Tie bow or tie
- 5 Apparatus (%)
- Lock and unlock braces
- Put on—remove slings
- Put on—remove splints
- Put on—remove corset
- Put on—remove braces
- 16 Utilities (%)
- Operate door bell
- Operate flip light

Small letter beside grade or symbol indicates:

- w Possible in wheel chair (Example: G w)
- b Possible in bed (Example: G b)
- No letter = Possible standing (Example: G)
- Grade with circle = Assistive, supportive or mechanical apparatus necessary for that grade (Example: (G))
- (Example: G√)
- ✓ Working on improving performance of activity
- Percentage of Independence in Each Section
- Count number of grades indicated for testing.
- Count number of independent grades.
- Divide number of independent grades by the number of grades indicated for testing to obtain the percentage of independence in each section or use percentage chart.

- Operate pull light
- Operate faucet
- Operate hook and eye latch
- Operate hasp and padlock
- Operate barrel bolt
- Operate inside door set
- Operate night latch
- Operate venetian blind
- Plug in cord
- Wind watch or clock
- Open and close drawers
- Open and close windows
- Use needle and thread
- Use scissors
- 6 Communication (%)
- Write or type test passage
- Handle own mail
- Handle money
- Use dial 'phone
- Use pay 'phone
- Wrap and unwrap package
- 24 Locomotion (%)
- Roll wheelchair on smooth surfaces
- Roll wheelchair on rough surfaces
- Control wheelchair down grade
- Roll wheelchair up grade
- Open common doors, go through, and close
- Operate automatic elevator
- Move on floor not in upright position
- Walk on smooth surfaces 100 yds
- Walk through an aisle of seats
- Walk on rough surfaces
- Walk up and down 20 degree grade
- Walk forward and backward carrying object
- Cross street with traffic light
- Get in and out of wheelchair
- Get in and out of chairs
- Get in and out of bed
- Get in and out of car
- Do 7 inch rise steps with rails
- Do 7 inch rise steps without rails
- Do plane steps
- Do bus and train steps
- Pick up object from floor
- Get down and up from floor
- Drive car
- Specialties

this apparatus. If necessary, specially designed assistive types of apparatus are made for the individual patient. It might be perfectly possible for one patient to achieve normal activity without any type of brace,

that actually teaching him to care for his own personal needs through the use of specially made splints or feeders will be his maximum functional capacity.

The fifth step is the attempt to evaluate

a patient, not only in terms of what he can do at the present but whether further treatment is necessary to increase his functional capacity and to assure his future security.

All patients regardless of involvement should be completely evaluated by the physiatrist and orthopedist before dismissal from the hospital. On the basis of this evaluation the present status and probable ultimate involvement should be thoroughly discussed with the patient and/or his family. Instructions in all necessary treatment to be continued at home can be given at this time as well as definite instructions in type and extent of activity and the time of the next medical check-up.

The sixth step is usually the return to a normal environment. Before this step is actually made both the patient and his parents should be fully acquainted with the patient's entire problem and the possibility of any change in his status in the future. In a great majority of patients treatment at home must be continued for many months, interspersed with repeated medical examinations to determine the need for additional treatment, either as a means of increasing the patient's functional capacity or perhaps minimizing certain deformities that seem to be occurring.

Thus a patient from the sixth block of a normal environment might return to the fifth block of evaluation and then be sent back into the treatment program, either for increased coordination and strength of muscle effort or for some phase of increased functional activity; or perhaps at this time he will be referred directly to the orthopedist for certain orthopedic procedures.

No medical program for the care of the after effects of poliomyelitis is complete unless it provides for adequate follow-up of its patients. Maximum return of strength, endurance and functional activity may require years of guided effort. Many deformities will not occur nor existing deformities progress until many years after the onset of the disease. Likewise, many

supportive, corrective and assistive orthopedic procedures cannot be carried out with optimum results until patients reach a period of solid bone formation. The doctor must maintain contact with his patient until maximum functional capacity has been obtained and future security established.

The seventh step is that of orthopedic surgery at which time the surgeon endeavors to determine whether certain procedures can increase the patient's ability to function with either greater effectiveness or endurance, but more particularly to determine whether the patient's increasing growth, height, weight and activity can be supported on weakened segments without damage to them. In a great many instances, before any consideration can be given to increased functional capacity and security, the orthopedic surgeon must correct deformities that have occurred during the convalescent period.

The continued physical security of the patient is the most serious responsibility of orthopedic surgery. It is absolutely necessary to foresee the effect of growth, increasing weight, age and activity on weakened bodily segments and to take adequate precautionary measures when relatively simple surgical procedures will prevent the occurrence of irreversible structural changes. Ideally, surgery should be considered not as a last resort after the damage is done but rather as a means of preventing these tragedies. It is obvious that the results obtained by the orthopedic surgeon depend on the thoroughness of the conservative care during the period of convalescence. Certainly, if fairly normal skeletal alignment and joint mobility have been preserved, the surgeon can do his work more efficiently.

It is essential that we foresee the possibility of later surgical procedures throughout all early phases of convalescence. It is equally important to point out that certain surgical procedures are needed during the convalescent stage. In general, it has been stated that when orthopedic surgery is indicated to correct a deformity, increase

functional capacity and assure future security of bodily segments, it should be deferred until the chronic stage or, in children, after bone formation is well advanced. This is only partially true. Relatively simple surgical procedures, such as sectioning of the iliotibial band or heel cord if done early in a convalescent program, often permit restoration of bodily alinement possible in no other way. This not only prevents irreversible and severely handicapping changes from taking place but also permits

more effective use of muscle re-education and functional training.

SUMMARY

To achieve restoration of maximum functional capacity possible within the limits imposed by the actual damage to the nervous system requires a logical sequence of treatment steps. Chronologically, this treatment program is well defined by the recovery rate expectancy curve and the age of the patient.

Public Health Considerations of Poliomyelitis*

JOSEPH G. MOLNER, M.D.

Detroit, Michigan

THE health officer is expected to control public health problems and it is his responsibility to the citizens of the community which he serves to do so, or at least to employ the best available knowledge and methods for the protection of the public health. When an epidemic of disease occurs, be it an epidemic of measles, of smallpox, of typhoid fever, or of poliomyelitis, an epidemic of a disease for which effective control measures are available or a disease for which there are no known control measures, the citizens naturally turn to him.

The methods for control, or rather attempted control, of those diseases which may occur in epidemic proportions and those diseases which are communicable have undergone many radical changes in recent years. Many restrictions, for example quarantine, were used not on the basis of scientific evidence but primarily because the ways and means by which diseases were spread were not known; often the utilization of quarantine was a grasp at the proverbial last straw. Despite the general tendency among public health workers of the present day to discredit and discontinue quarantine as a method of control during an epidemic of disease the community often demands the institution of this procedure. Here is a method which is familiar, which had been used for many years with apparent official approval and the health officer through the force of public opinion and to allay anxiety is virtually forced into the adoption of an only potentially valuable control measure of limited practical applicability.

In spite of pressure groups of any type it is one of the first and most important

functions of the health officer to weigh preventive procedures on the basis of available scientific facts. He is in a difficult position, however, because frequently much publicized information emanates from the scientific laboratory, from the desk of the epidemiologist or the office of the clinician and the information may be related only remotely to the prevention of disease. The public is apt to accept such information without question as a panacea and the health officer is expected to apply the panacea within his jurisdiction. Admittedly, the health officer has in addition to the responsibility for weighing the potential need of preventive measures, the responsibility for the field evaluation of such measures. However, before embarking upon their adoption, even on an experimental basis, these procedures must be weighed carefully and studied for their probable value as preventive measures, relative ease of enforcement and economic effect upon the individual, the household and the community. If such measures are found to be administratively sound and financially practical, they should be put into effect as the policy of the organization, as an epidemiologic supplement or as administrative research.

Just what should the health officer do when poliomyelitis strikes?

EDUCATION

Certainly one cannot help but believe that of the many dangerous diseases poliomyelitis appears to have the most adverse psychologic effect on the public, and it is the responsibility of the health officer not only to alert the public, including

* From The Detroit Department of Health, Detroit, Mich.

physicians, to the increased incidence of the disease but to gear the health education services of his organization to present authentic information and to prepare and submit it in a manner which will most effectively avoid panic and allay anxiety.

Satisfactory Press Relations. The public press and the radio represent two of the most important outlets for lay information, and a cooperative press releasing facts instead of fancy about poliomyelitis is of inestimable value. The health officer must secure proper contact with the press and prepare information concerning the disease in an intelligent and understandable form. The press is always anxious to carry facts and when misinformation is printed it is because of misunderstanding rather than misrepresentation. We know that a press which dramatizes or exaggerates facts can create anxiety and cause a great deal of damage. It is therefore of paramount importance that the health agency secure the cooperation of the press. This may, of course, be accomplished most satisfactorily by making available to the news gathering agencies properly prepared information in a language which their readers can readily understand.

Alerting the Public. There are many other ways of alerting the public to the significance of an epidemic of disease. To illustrate a few of these we need to mention parent-teacher associations, mothers' clubs, health guild and, of course, the radio and possibly television.

Contrary to the old attitude, there is very little information concerning the communicability, clinical significance, complications and treatment of disease which cannot be made available to the thorough understanding of the public if such material is properly prepared and presented. It is this fuller knowledge of sickness which stimulates greater cooperation.

Informing the Physician. It is with no embarrassment that physicians admit the need for information concerning poliomyelitis. With the relatively low rural epidemic attack rate and even lower urban attack

rate, with the relative infrequency of epidemics, it is not very often that a physician is called to see a patient or a suspicious case of poliomyelitis.

It is considered important that the physician be in a position to answer the questions directed at him by his patients, and it is important especially during the time of an epidemic that the information released from the official health agency be coordinated with the information which patients receive from their family doctors; contradictory answers or apparent disagreement between the physician and the health agency tend to create lack of confidence in both. The physician, therefore, must have the facts concerning poliomyelitis at least at the same time, preferably before, the information is given to the public.

The physician's lack of experience with poliomyelitis may lead to an inadequate appreciation of the real significance of the disease. The health officer must therefore confer with local physicians early in an epidemic and discuss the facts related to poliomyelitis as a disease and as an epidemic afflicting the community.

To inform physicians concerning poliomyelitis, or any public health problem, postgraduate conferences are of inestimable value. Conferences of this type should be conducted under the auspices of the local medical society, the health department and any interested unofficial agency. This type of conference has been in existence in many parts of the United States for many years and has been exceptionally well patronized by the medical profession. Speakers generally include members of the local medical society, the local health officer and at times authorities from other sections of the country.

Not all the essential information concerning the medical and public health aspects of poliomyelitis can be presented in conferences of this type nor can it be expected that all physicians will attend. Therefore, published information directed toward the physician either in local official publications or through communications

from the health department should supplement the conferences.

The health services of a community should also be geared to lend consultation to the private practitioner of medicine in the diagnosis and treatment of disease. Diagnostic services, in addition to clinical consultation, should, of course, include laboratory facilities for aid in diagnosis.

The agenda for education of the physician must include the most recent and best information concerning the epidemiology of the disease, for example, probable sources of infection, probable modes of transmission, incubation period, susceptibility and prevalence. There must be included in these discussions the criteria of early diagnosis, the significance of paralytic and non-paralytic disease and the need and significance of laboratory methods for the diagnosis of poliomyelitis. It must be emphasized that during an epidemic all cases of unexplained fever or other symptoms which may be related to poliomyelitis should be regarded with extra care lest they be the signs and symptoms of non-paralytic poliomyelitis.

The clinical classifications of poliomyelitis and the significance and value of the latest and most modern therapeutic regimens should also be presented, with proper emphasis placed upon those proposed and sometimes publicized therapeutic measures which may be of only potential value or of no value. It is important that the physician know of the community facilities which are available for the care of those with acute cases of poliomyelitis as well as the complications of the disease.

From the public health point of view it is appreciated that all cases diagnosed either as suspicious or actual cases should be reported to the health agency. The significance of this reporting must also be called to the attention of the physician.

PREVENTION

No phase of communicable disease control is of greater importance to the public and to the physician than those measures

which will prevent or which may modify disease. During an epidemic of poliomyelitis there is more misinformation concerning this public health aspect of the disease than any other. The preventive phases of poliomyelitis must be stressed to the physician and to the public.

The significance of early recognition and isolation of active and suspicious cases and the importance of the carrier state in poliomyelitis, together with the relative ineffectiveness of quarantine measures, should also be given special consideration. It is only proper with our most recent knowledge concerning the discharge of the virus from the human body that human excrements be properly removed from potential intimate contact with the human population. No major changes are necessary in community facilities for the collection or disposal of human excreta but certainly proper and careful disposal of excreta within the isolation area is indicated.

Because flies may play an important role in the transmission of the disease and because the protection of food from flies is an essential public health measure, screening of homes, destruction of flies and protection of food from flies should be recommended.

Since person-to-person contact is probably the most important of the many proposed theories of the mode of transmission of the disease and because circumstantial evidence strongly supports this proposal, it should be recommended that persons, particularly children, do not travel to or from the epidemic area. The closing of community borders, schools and churches is not recommended; by the time such measures are initiated the seeding of infectious agents in the community or in the area would be so extensive that at best they would be only gestures or futile attempts.

However, in the event that poliomyelitis occurs in epidemic proportions at the time that schools are to be opened it may be considered a measure of expediency to delay their opening. It is considered expedient to protect children so far as practi-

cable against unnecessary contact with persons outside their homes, and it is recommended therefore as good practice during an epidemic of poliomyelitis to keep children away from swimming pools, wading pools, theaters and churches. There is reasonably good evidence to indicate that trauma, exertion and fatigue may predispose to poliomyelitis and avoidance of these conditions should also be recommended.

Of the many proposed preventive measures there is probably none more important than deferment of elective tonsillectomies or elective operations of the nose and throat during an epidemic or just preceding expected high incidence or epidemic proportions of poliomyelitis since there is good evidence to show that recent tonsillectomies are predisposing to bulbar poliomyelitis. Emergency tonsillectomies must be left to the discretion of the family physician.

NURSING VISITS

A well co-ordinated program in public health calls for nursing visits to the homes of patients. These are not for the purpose of caring for patients because all poliomyelitis patients should be cared for in hospitals. Public health nursing calls are made primarily to consult with the families of patients and to lend assistance in any way possible. The public health nurse as a family health counsellor in these situations can be of invaluable service.

HOSPITALIZATION

Treatment of infantile paralysis with modern methods is complicated and expensive. Hospital care is essential and hospital facilities for the care of poliomyelitis should be available in every locality. This poses a very important problem for the health administrator because in spite of the generally admitted theories that poliomyelitis is not a highly communicable disease, that the secondary attack rate is virtually negligible and that patients may be cared for in general hospitals, most general hospitals resist admission of poliomyelitis patients for fear of institutional epidemics.

There is, therefore, need for education of the hospital administrator as well as the medical staff of the institution to the fact that poliomyelitis can be cared for without unusual risk in general hospitals during the acute as well as during the convalescent stages. Poliomyelitis patients can certainly be cared for in general hospitals without risk to other patients and personnel if the usual precautionary measures used in the care of other types of diseases are invoked. Such care implies isolation precautions, reasonably careful technic in handling of the patient and proper disposal of excreta.

The health department, in cooperation with the medical profession and with other official and non-official agencies, must be the driving force if not the supplier of adequate medical care for poliomyelitis patients. Needless to say, it is preferable that the health department be the driving force in making adequate care available.

This will involve availability of hospital facilities for care of the patient during the acute stages and equipment and materials for administration of the most modern methods of therapy. Under present methods of therapy equipment such as respirators, hot pack machines and physical and occupational therapy equipment for the convalescent care and rehabilitation of patients is required.

Proper care of patients will include well trained personnel conversant with modern therapeutic measures and physical therapists properly trained in administration of newer treatments. It is important to have occupational therapists well versed in the problems of the convalescing poliomyelitis patient and the means by which these patients may be brought back to the ultimate of self-sufficiency and productiveness. This may necessitate special training for the available personnel or the recruitment of new personnel who have been trained in the care of poliomyelitis patients.

The health department has an important responsibility in the promotion of available and good care for poliomyelitis patients regardless of their economic status.

Modern and effective methods for the treatment of poliomyelitis have pyramided the cost of medical care to the point where such service is virtually beyond the reach of the majority of the population. In many states funds are available through official organizations and funds may be made available through non-official agencies, but the important thing is that care, regardless of the source of financing, must be available for the patient.

Many treatment phases of poliomyelitis do not require professional personnel. With the shortage of professional personnel, lay persons can be trained to apply hot packs and to administer the simpler types of physical therapy.

EPIDEMIC COMMITTEE

In keeping with the thought that a well informed community is a cooperative community, it has been found expedient to organize at the time of an epidemic a citizens' committee to assist in the management of the various problems which arise and to assist in the dissemination of information concerning poliomyelitis and the epidemic in existence. A committee of this type, composed of leaders in the community, for example, ministers, teachers, attorneys, bankers and public officials, can do a great

deal in disseminating reliable information concerning the epidemic, procurement and even training of personnel and procurement of hospital beds and equipment.

Citizen committees of this type have been organized on several occasions during an epidemic of poliomyelitis and have functioned very successfully. It must be emphasized, however, that these committees must be working committees rather than figure-heads—committees in name only can be obstructive.

CONCLUSIONS

The public health considerations of poliomyelitis herein discussed are for the most part non-specific. There are but very few specific preventive measures which can be applied or effectuated as far as the public health aspects of poliomyelitis are concerned. The measures presented, however, are quite generally accepted and represent the best judgment of many public health officials and research workers. Until such time as the epidemiologist, the laboratory worker or the clinician make available to the public health officer more specific means of control, such as active or passive immunization, the public health approach with probable modification will remain much the same as outlined in this paper.

End of Symposium on Poliomyelitis

Adrenal Medullary Tumor (Pheochromocytoma)*

FRANCIS N. HATCH, M.D., VICTOR RICHARDS, M.D. and RALPH J. SPIEGL, M.D.

San Francisco, California

PHEOCHROMOCYTOMAS are tumors of the chromaffin cells of the adrenal medulla. These cells are derived from the neuroectoderm of the neural crest and are developmentally related to the matured cells of the sympathetic ganglia. Paragangliomas are tumors of the paraganglia, aggregates of chromaffin cells found apart from the adrenal medulla in association with the ganglia of the sympathetic trunk and plexuses and occasionally in relation to viscera where they may have arisen in common with the peripheral sympathetic ganglionic groups; they may also arise from the coccygeal or carotid bodies. Few paragangliomas are true chromaffin-cell tumors, and they rarely produce cardiovascular symptoms. Pheochromocytomas, in contrast, have been aptly described as histologically benign but physiologically malignant; most of them cause either paroxysmal or sustained hypertension.

Adrenal pheochromocytomas are usually encapsulated, small, round and unilateral; however, they may be large (reported up to 12 cm. in diameter and weighing 2,000 Gm.) and bilateral (16 of the 152 cases reported by MacKeith).¹ If malignant, metastases are most frequently found in the regional and thoracic lymph nodes, liver and skeleton. The very large tumors are frequently cystic and hemorrhagic. The granules of the tumor cells give a characteristic brown "chromaffin" reaction when stained with chromium salts. Adrenalin assays of the tumor tissue have varied from 0.12 to 20.0 mg. per Gm.;² the normal adrenal medulla contains about 0.4 mg. of epinephrine per Gm.

In 1886 Frankel³ reported finding bilateral adrenal tumors at the autopsy of an eighteen year old girl. Labbé, Tinel and Doumer⁴ wrote the first detailed clinical-pathologic description of the associated paroxysmal hypertension in 1922. A correct clinical diagnosis was reported in 1926,⁵ but the first experience in preoperative diagnosis, successful excision and symptom-free survival was not described until 1929.⁶ In 1937 increased amounts of epinephrine were demonstrated in the blood of patients during attacks;⁷ MacKeith¹ in 1943 reviewed the reports of 152 patients with adrenal pheochromocytoma and nine with paraganglioma associated with the adrenal-sympathetic syndrome. Since his paper appeared, at least twenty-six additional cases have been described. The best reviews of the subject are those of Belt and Powell,² Howard and Barker,⁸ McKenzie and McEachern⁹ and MacKeith.¹

CLINICAL MANIFESTATIONS

Pheochromocytomas are found equally distributed in both sexes, most commonly during the third to fifth decades and more frequently in the right adrenal. As stated by MacKeith these tumors may cause "(1) Recurrent paroxysms of generalized vasoconstriction accompanied by a remarkable but transient hypertension—the *adrenal-sympathetic syndrome*; (2) chronic hypertension with renal and cardiac failure, resembling malignant hypertension; (3) Addison's disease from local pressure on the cortex, an uncommon picture, or (4) no symptoms." Hirsutism, precocious genital development and other evidences of adrenal cortical

* From The Departments of Medicine and Surgery, Stanford University School of Medicine, San Francisco, Calif.
MAY, 1949

disturbance have been reported.¹⁰ Those cases of sustained high blood pressure may resemble essential hypertension from the onset. Patients with typical hypertensive crises early in their clinical course may enter a later stage of continuous hyper-

Vasoconstrictive effects—cramps, colic, etc.—may begin in the lower part of the body and progress cephalad to cause successive anginal constriction, dizziness and severe headache. During severe episodes the patient is unmistakably ill and the attack may terminate in a state of shock. Blanching and pallor of the face and extremities are common although there may be alternate flushing or no obvious color change of the skin. Tachycardia, bradycardia and irregularities of rhythm may occur. The pulse is usually weak. Accentuation of the aortic second sound and transient aortic diastolic murmurs have been noted. The systolic blood pressure may rise 100 to 200 mm. of mercury above the interim levels, with an associated diastolic increase. During attacks there may be dilatation of the pupils. Hyperglycemia and glycosuria are other effects of increased discharge of epinephrine. In about one-third of the cases a tumor is palpable in the abdomen or flank. Massage of such tumor, or of the loin or abdomen if a palpable mass is not present, may induce an attack. It should be emphasized, however, that failure to cause an attack by this means does not preclude the diagnosis of chromaffin-cell tumor; furthermore, if a mass is not felt, an attack may be induced by massage but this is not to be taken as evidence that the tumor is on the side of the abdomen manipulated. (Table II.)

TABLE I
FREQUENCY OF OCCURRENCE OF PRINCIPAL SYMPTOMS
IN EIGHTEEN CASES OF PHEOCHROMOCYTOMA
(Howard and Barker, 1937)

Symptoms	No. of Cases
Blanched, cold extremities	17
Palpitation	17
Nausea	16
Sweating	14
Vomiting	13
Headache	10
Pulmonary edema	9
Precordial pain	8
Dilated pupils	4
Body tremors	3
Dizziness	2

tension. In some, paroxysms are superimposed upon a state of persistent hyperpiesis. The patients with paroxysmal attacks are clinically most common, most readily recognized and therapeutically most hopeful. The history may indicate attacks over as long as sixteen years. The initial attack may be as severe as subsequent episodes, but often the early symptoms are mild and equivocal: transient malaise, headaches, nausea, vague pains or dizziness may recur unexplained until typical crises suggest the diagnosis. Attacks may occur only at long intervals or as often as several times a day.

Crises are characterized by sudden, generalized vasoconstriction that produces both local and generalized effects. Table I, listed by Howard and Barker⁸ from a review of eighteen cases, is representative of the described symptomatology of reported series. MacKeith¹ described the clinical variations in detail. Some patients experience symptoms limited to only one region, such as episodic abdominal pain and vomiting, or recurrent headaches. Brief antecedent malaise or paresthesias may initiate the attack. Palpitation is usually the first symptom, but vague uneasiness, lassitude, weakness or regional pain in the abdomen, chest or head may provide the subjective warning.

Attacks may last for a few minutes or persist for hours or days. In at least half the cases crises occur spontaneously, but in many instances one or more precipitating factors have been noted. These include postural changes (most commonly), nervousness, emotional stress, physical exertion, pain, constipation and menses. Clinical complications are dependent upon degree and duration of the induced hypertensive state. Progressive alterations include arteriosclerosis, cardiac hypertrophy, retinal and renal damage; acute effects which account for sudden fatalities are pulmonary edema, cerebral hemorrhage and shock.

Differential Diagnosis. The diagnosis of pheochromocytoma may be obvious in the

observed presence of typical paroxysms with the rise of blood pressure and attendant objective vasomotor manifestations. If a palpable tumor is also present or attacks may be induced, the evidence is conclusive. The absence of clearly defined attacks does

given intravenously caused hypertensive crises with the signs and symptoms of paroxysmal sympathetic attacks. This experience has provided a simple clinical test for chromaffin-cell tumors. Histamine base, 0.025 or 0.05 mg., given intravenously

TABLE II
BLOOD PRESSURE OBSERVATIONS IN EIGHTEEN CASES
(Howard and Barker, 1937)

Case	Age	Sex	Duration of Symptoms	Blood Pressure —Resting	Blood Pressure —In Attack
1	28	F	Several months	150/100	260/180
2	30	F	1½ yr.	130/82	+300/180
3	37	M	1 yr.	140/80-210/130	+300/180
4	29	M	10-11 yr.	160/100	300/?
5	26	F	10 yr.	120/90	260/120
6	39	M	6 mo.	110/?	+200/?
7	46	M	9 yr.	160/120	280/120
8	29	M	1½ yr.	150/115	325/200
9	41	M	1½ yr.	200/100	340/110
10	36	F	5 mo.	125/105	300/240
11	16	M	5 mo.	125/105	300/200
12	45	F	7 yr.	170/80	+300/240
13	40	F	11 yr.	185/105	290/160
14	45	M	7 mo.	140/90	+260/120
15	37	F	7 yr.	100/60-130/90	220/130
16	38	M	17 mo.	225/160	330/120
17	69	M	3 yr.	112/70	260/120
18	27	F	4 yr.	120/80	240/180

not invalidate the diagnosis but forces other considerations. These are grouped in Table III in categories of diagnostic probability.

LABORATORY TESTS

The patient suspected of having a pheochromocytoma is routinely subjected to many laboratory and a few clinical tests. These are briefly tabulated in Table IV. Negative or equivocal results are frequent. The most specific test is the demonstration of increased amounts of epinephrine in the blood during or even between paroxysms.¹¹ This is cumbersome and the test is not always positive even in the presence of the tumor. The histamine test was first described by Roth and Kvale.¹² This test was based on the assumption that the opposing physiologic effects of histamine and epinephrine might be utilized during the surgical excision of pheochromocytoma to prevent responses to the excessive epinephrine blood levels provoked when the tumor is handled. However, a contrary effect was produced; very small amounts of histamine base

TABLE III
DIFFERENTIAL DIAGNOSIS IN CASES OF PHEOCHROMOCYTOMA

Likely

Essential or malignant hypertension
Acute and chronic nephritis
Hyperthyroid state
Cushing's disease
Polyglandular dyscrasia
Brain tumor
Mediastinal tumor

Unlikely

Diabetes mellitus
Angina pectoris
Peptic ulcer
Tabetic crises
Migraine
Epilepsy
Periarteritis nodosa

Confusing

Neurasthenia
Anxiety state
Cardiac neurosis

will cause a systolic pressure rise of at least 100 mm. of mercury if the tumor is present. Headache and the usual sympathetic symptoms may be severe and the effects last as long as ten minutes in some cases. The test has been positive in 100 per cent of the few cases described to date.¹³

More recently a similar test utilizing the "adrenolytic" action of benzodioxane drugs has been reported. In May, 1947 Snyder and Vick¹⁴ described the use of this diagnostic aid in two children with pheochromocytoma. Goldenberg, Snyder and Aranow subsequently presented a detailed discussion of the drugs and the test, with a report of two additional cases.¹⁵ The structural formulas and pharmacologic relationship between the adrenolytic benzodioxanes and the sympathomimetic phenylethylamine are indicated in their paper. Fourneau and Bovet¹⁶ first investigated the benzodioxanes. Many chemical variants were tested; those selected for clinical trial because of their minimal toxicity are designated 1164F ([2,4,-dimethylpiperidyl]

methylbenzodioxane), 933F (piperidyl-methyl benzodioxane) and 1071F (dimethyl-aminomethyl benzodioxane).

The basis for use of these drugs is that in non-toxic dosage their action is adrenolytic rather than sympatholytic. Thus in the

TABLE IV
LABORATORY AND CLINICAL TESTS IN THE DIAGNOSIS
OF PHEOCHROMOCYTOMA

1. Epinephrine: increased blood level during or between attacks
2. Histamine: 0.025–0.050 mg. of base intravenously: symptomatic simulation of paroxysm; rise in systolic blood pressure 100 mm. Hg or higher
3. Benzodioxane drugs (Fournau): "adrenolytic agents," intravenously: rapid fall of systolic and diastolic blood pressure
4. Glucose tolerance test: decreased tolerance, impaired carbohydrate metabolism; frequently normal
5. Basal metabolic rate: to exclude hyperthyroid state; may be greatly elevated by pheochromocytoma²⁰
6. 17-ketosteroid excretion: inconsistently affected by adrenal medullary tumor
7. X-ray demonstration of adrenal tumor: excretory or retrograde pyelography which may fail; perirenal air insufflation which is more reliable but hazardous
8. Electrocardiogram:

abnormalities of rhythm conduction defects altered T waves shifts of axis	}	nothing characteristic
--	---	------------------------

presence of pheochromocytoma the attendant increase in circulating epinephrine is counteracted and a fall of blood pressure effected; in hypertension from other causes, including "essential hypertension," a minimal effect, no effect or a purely pressor response is produced. Normal subjects respond with a mild pressor effect.

The technic for using these drugs and interpreting the test is detailed by Goldenberg et al.¹⁶ A continuous intravenous drip of normal saline is given to the unsedated patient during the rest period preceding introduction of the drug. The dosage used was 10 mg. of 933F or 30 mg. of 1164F per square meter of body surface given over a two-minute injection period while the intravenous drip continued. The duration of the drug action was usually less than fifteen minutes. Blood pressure readings were taken at frequent intervals before, during and after drug injection, until the pressure returned to the pre-administration levels. Interpretation of results was facili-

tated by plotting the pressure changes against time. In three patients with pheochromocytoma the maximal reduction of systolic and diastolic pressures was from 50 to 70 mm. of mercury; pre-injection pressure levels were regained in about fifteen minutes.

Side actions of the benzodioxane drugs were not serious. They included sinus tachycardia, flushing, palpitation, nervousness, cold and clammy extremities, hyperpnea, mild headache, fright, sighing respiration and dizziness. This test is therefore preferable to the injection of histamine from the subjective standpoint. The use of neither test has yet produced a seriously untoward response but the reported series for each is small, and the danger of inducing either a marked rise or fall of blood pressure in the hypertensive subject should not be forgotten.

TREATMENT

Pheochromocytomas are treated by surgical excision; there is no medical therapy except ancillary in preoperative and postoperative care and palliative during paroxysms. Morphine or codeine, sedatives, and vasodilator drugs may be helpful in an attack. Phlebotomy and lumbar puncture have been suggested for prolonged episodes. MacKeith states that epinephrine is specific in treating postparoxysmal collapse.

Pre- and postoperative care have been fully discussed by Biskind, Meyer and Beadner¹⁷ in a review of all patients treated surgically to 1940. Because these tumors are frequently accompanied by adrenal cortical deficiency, they recommend a high salt diet with 4 Gm. of additional salt by mouth for two days, 5 mg. of desoxycorticosterone intramuscularly the day before and the day of operation and the injection of 10 cc. of adrenal cortical extract during excision and as needed in the postoperative period. The choice of anesthetic seems to be induction with avertin or tribromethylene followed by ether-nitrous oxide inhalation. Spinal anesthesia is contraindicated. Sharp fluctuations of blood pressure during the operation are controlled

with epinephrine or neosynephrine subcutaneously or intravenously and amyl nitrite inhalation. Intramuscular injection of epinephrine in oil may be an aid for sustained effect.

SURGICAL CONSIDERATIONS

Approximately 10 per cent of adrenal medullary tumors are bilateral. In a fair proportion of cases it is impossible to ascertain either from clinical signs or diagnostic technics on which side the tumor is present. These factors lead us to favor a bilateral, simultaneous exploration of the adrenals. In sympathectomy for essential hypertension exploration of the adrenals is achieved by either splitting the diaphragm radially for a short distance or, recently, by pushing the diaphragmatic attachments off the vertebral bodies to a degree sufficient to expose the retroperitoneal tissues. In cases in which one suspects an adrenal tumor and is not contemplating sympathectomy, a technic comparable to that described by Young¹⁸ is advocated. This permits bilateral, simultaneous exposure of both adrenals through separate retroperitoneal incisions. In order to shorten the operative time and achieve really simultaneous exploration it has been our custom to utilize two surgical teams. The patient is placed in a prone position upon the operating table. Paravertebral incisions are made about 6 to 8 cm. lateral to the spinous processes, centering the incision just below the twelfth rib. The latissimus dorsi musculature is divided in the line of the incision, exposing the serratus posticus inferior muscle which in turn is divided in its lower portion. The conjoined portion of the lumbodorsal fascia is incised just lateral to the sacrospinalis musculature and the retroperitoneal tissues exposed. The costovertebral ligament of the twelfth rib may be incised and the rib retracted upward for greater exposure. If necessary for a large tumor, some of the twelfth rib may be resected. The retroperitoneal fat is stripped off, thereby exposing Gerota's fascia which envelops the kidney and adrenal. An opening is made in Gerota's

fascia over the adrenal, permitting its delivery and complete exploration.

Surgical Results. Data for the results listed in Table v are taken from the reviews of Biskind, Meyer and Beadner¹⁵ (1939), MacKeith¹ (1943) and all cases reported

TABLE V
SURGICAL RESULTS

Dates	No. Cases	Successful (per cent)	Fatal (per cent)
1929-1936	19	12 (63)	7 (37)
1936-1943	18	15 (84)	3 (16)
1943-1947	20	17 (85)	3 (15)

since 1943, including the three added in this paper. Since 1943, twenty-four cases have been reported (including ours). Although three of these patients died during operation for adrenal tumor, four died who were not treated surgically; two patients unsuspected of having pheochromocytoma died during or shortly after operation for other conditions.

Follow-up. Those patients who survived operation and the postoperative period have had full recovery from their paroxysms. Preoperative pathologic changes referable to sustained hypertension regressed with the re-establishment of persistent normal blood pressure. Some patients have been followed from seven to ten years.¹⁹ The outcome has not been so favorable in the rare cases in which the adrenal tumor was malignant.

Between January, 1944 and December, 1946, three patients with pheochromocytoma were seen at the Stanford Hospital and Stanford University Medical School Out-Patient Clinics.

CASE REPORTS

CASE I. Mrs. J. C., a twenty-three year old white housewife, had a negative medical history until the onset of her present illness in December, 1943. She was seen in a prenatal clinic in September with a normal eight-weeks' pregnancy. Blood pressure readings were 100/60 to 105/70 on three occasions from October to December. On December 22nd, after some nose-bleeding,

the pressure was 200/120 to 220/130. There was moderate albuminuria and toxemia of pregnancy seemed likely. A Cesarean section was performed in another hospital in early January, 1944, but because the blood pressure remained high the patient entered Stanford Hospital on the clinic service January 21st. Physical findings included a blood pressure of 250/140, papilledema, retinal hemorrhages, narrowed retinal arteries, moderate enlargement of the heart to the left and an apical systolic murmur.

Laboratory findings were as follows: Blood counts were normal. Timed urine specimens were fairly constant: specific gravity, 1.010; pH, 7.0; protein, 1.2 Gm./24 hours; red blood cells, 3,000,000; white blood cells, 3,000,000; hyaline casts, 100,000; granular casts, 300,000. Repeated fasting blood sugars were from 95 to 100 mg. per cent. Spinal fluid, serum proteins, urea, creatinine and chlorides were repeatedly normal. X-rays of the skull, chest and abdomen, and excretory pyelograms were negative.

Differential diagnosis included malignant hypertension of unknown cause, placental neoplasm and intracranial lesion.

Dilatation and curettage recovered only normal placental remnants. On January 25th she had an intracranial hemorrhage followed by restlessness, headaches, epigastric distress, back pain and further diminution of vision. There were no typical paroxysmal increases of blood pressure although these symptoms were occasionally accompanied by a moderate rise from the usual range of 230/130 to 260/160. Continuation of the listed complaints led to a splanchnic section on February 16th. During this operation the adrenal glands were not explored. Operative and postoperative hypotension was controlled essentially with neosynephrine injections. The lowest pressure of this time was 114/98, and it rose to 200/120 within three days after operation. Adrenal pheochromocytoma was first considered after prompt restoration of hypertension. The patient had a fatal cerebral hemorrhage on March 17, 1944, only three months after the first signs of high blood pressure.

Autopsy revealed that the pheochromocytomas were small, bilateral, intra-adrenal; that on the right, 3.5 by 1.7 cm., replaced almost the entire gland. Generalized arteriosclerosis was present. The heart was 340 Gm., the left ventricle was 20 mm. thick and the coronary arteries were patent but contained atheromas.

The brain revealed a recent hemorrhage into the pons, cerebral peduncle and fourth ventricle. The liver and kidneys showed no changes typical of toxemia of pregnancy but the kidneys were altered by the hypertension; small renal arterioles showed marked hyaline thickening of their subintimal layers, with fatty degeneration and poor cellular detail; the slightly larger arterioles had reduplication of the inner elastic membrane. The ascending arch and the thoracic and abdominal portions of the aorta had marked atheromatous changes with plaques 2 to 3 mm. thick. There were small plaques in the renal arteries.

Comment. This patient presented not only the usual diagnostic problem of sustained hypertension in a young person but added the tempting consideration of its relation to her pregnancy. As the first of the series she did not have the benefit of adrenal exploration at the time of splanchnicectomy; since she was of the 10 per cent group who had bilateral pheochromocytomas, the importance of the oversight may be questioned although the left tumor was small and the cortex there was not affected. It is of considerable interest that she had so much arteriosclerosis and left ventricular hypertrophy with hypertension of only three months' duration.

CASE II. Mrs. E. P., a thirty-two year old white housewife, had a negative past medical history except for suspected hyperthyroidism in 1935 when she had a mild tremor and a blood pressure of 130/80. In December, 1944 she entered another hospital at term and in labor; her blood pressure was 210/155. Following a normal delivery, the blood pressure was 125/85 but soon returned to high levels which were uninfluenced by the usual medical treatments. There was mild to heavy albuminuria. As an out-patient during the next two months she continued to have marked hypertension, tachycardia, nervousness and headaches; the basal metabolism rate was +19 to +43, with normal blood cholesterol levels. Her ocular fundi showed evidence of slight bleeding and exudation and she had an episode of moderate left heart failure. Subtotal thyroidectomy in March, 1945 failed to reduce the basal metabolism rate or alleviate her symptoms. Because of severe left ventricular

failure, she was sent to Stanford University Hospital where she was admitted on the clinic service April 21st. Examination confirmed the changes in the retinae, the blood pressure was 170/140 to 140/110, the heart was enlarged and there was a loud systolic precordial murmur with gallop rhythm and pulmonary congestion. The cardiac status improved with therapy but the moderate left failure persisted and fresh retinal hemorrhages appeared during the next two to three weeks.

Laboratory examination revealed the following: Blood was normal; urine: specific gravity was 1.012 to 1.010, and there was 0.69 to 6.9 Gm. albumin in the twenty-four-hour specimens on repeated tests. Fasting blood sugar levels were 121, 131 and 160 mg. per cent; urea, 15 to 18 mg. per cent; chlorides 530 mg. per cent; cholesterol, 204 mg. per cent and plasma proteins, 5.8 Gm. per cent. The basal metabolic rate was +40. X-rays showed enlargement of both right and left ventricles of the heart, an enlarged left auricle and full pulmonary conus; excretory pyelograms were normal. Repeated electrocardiograms were taken; the only significant finding was a marked left axis deviation that shifted toward normal after the patient's operation.

Differential diagnosis considered the relationship of the hypertension to a post-toxicemic complication, a primary renal lesion, retained placental tissue, the problem of an intrinsic myocardial affection and cardiac disease dependent upon thyrotoxicosis.

The blood pressure fluctuated from 140/110 to 170/130, with occasional increasing nervousness, tachycardia and perspiration but no clearly recognized attacks of paroxysmal hypertension. By May 19, 1945, the cardiac failure was sufficiently controlled to allow a bilateral splanchnicectomy and exploration of the adrenals.

After anesthesia was established with intratracheal ether and oxygen the patient was turned to the prone position and at once sank into profound shock which was corrected with whole blood transfusion and neosynephrine injections. Bilateral incisions allowed simultaneous operative procedure but the right adrenal gland was first exposed and, because it was definitely enlarged, three-fourths of it was excised before the left gland was examined. The left adrenal contained an unmistakable tumor which was removed, leaving about one-third of the unaffected gland *in situ*. Routine bilateral splan-

nicectomy was then performed. Pathologic examination of the adrenals showed that the tissue from the right gland was normal while the left contained a typical pheochromocytoma. Adrenal cortical extract in large amounts was given intramuscularly during the operation and routinely for nine postoperative days. Neosynephrine and epinephrine in oil supplemented against hypotension. The blood pressure was 160 to 180 systolic at the start of operation; it dropped to 80 during the mentioned period of shock and rose to 170 at one point during the procedure. The blood pressure stabilized in the range of 95/50 to 110/80 postoperatively and was 100/75 at dismissal five weeks later. Signs of cardiac failure cleared steadily.

When the patient was last examined in May, 1946, one year after her operation, the blood pressure was 110/85, the ocular fundi showed no retinopathy and there were no heart murmurs or evidences of cardiac enlargement. In correspondence in August, 1947 she stated she had felt quite well to date.

Comment. This patient's history again raised the problem of the relationship between her hypertensive state and possible toxemia of pregnancy. The elevated basal metabolic rate and diagnosis of moderate hyperthyroidism ten years earlier required consideration of thyrotoxicosis; absence of other evidence of thyroid disease and the probability that the basal metabolic rate was affected by her cardiac failure were against this. Other reviews have cited instances in which a greatly hypertrophied adrenal gland has been mistaken for an adrenal tumor. The satisfactory course for over two years postoperatively suggests that the patient is completely relieved of her hypertensive state. Splanchnicectomy must be considered in evaluating her course.

CASE III. E. G., a twenty-six year old white physician, was seen on November 13, 1946, with the complaint of "paroxysmal hypertension" of two-years' duration. His past history included chronic frontal sinusitis treated surgically and paroxysmal auricular tachycardia since the age of ten. The latter had been proved by electrocardiogram, was readily controllable and was clearly distinguished by the patient from the attacks described in his present com-

plaint. Two years previously he had first noted episodes of sudden tenseness, nervousness, tachycardia and palpitation associated with tremor and profuse perspiring as the attacks subsided after two to five minutes. There was pupillary dilatation during some attacks but blanching or pallor of the skin was not noted. There were no recognized provocative factors except that attacks had occurred occasionally when he rolled over in bed. Attacks increased in frequency from one every two to three weeks to one or more almost daily; they varied in intensity and duration. An episode in June, 1946 initiated a violent headache. Subsequent attacks were associated with similar occipital pain, often too severe to be eased by narcotics and which lasted five minutes to fourteen hours after the paroxysm had ceased. Complete neurologic study, including skull films, electroencephalogram and cerebrospinal fluid examination, showed no evidence of an intracranial lesion.

While stationed at a U. S. Naval hospital in the following three months, the patient thoroughly studied his case. His usual blood pressure varied from 130/70 to 150/90, but when taken during several typical attacks it was in the range of 200 to 220/110. The following examinations were normal: blood count, urinalyses, serology, serum cholesterol, glucose tolerance, cold pressor test, electrocardiogram, x-rays of skull, chest, sinuses and excretory pyelograms. Blood sugar levels during attacks were variable. Intravenous insulin, 0.1 unit per Kg. body weight, reduced the fasting venous sugar from 78 to 44 mg. per cent, caused a moderate insulin reaction but did not induce a paroxysm. Epinephrine, 0.2 cc. of 1:100,000 intravenously caused symptoms precisely simulating those in an attack. The basal metabolic rate was +3 and +8 on two tests.

He entered Stanford Hospital in November, 1946, for confirmation of his own diagnosis of pheochromocytoma. Physical examination revealed a husky and apparently healthy young man. The retinae were normal, the lungs clear, the heart normal in size, regular and without murmurs. Blood pressure readings varied from 130/90 to 180/110. The abdomen was normal and massage of the belly and flanks did not produce an attack. No severe paroxysms occurred spontaneously during this period. X-rays and other studies were repeated and found normal. The twenty-four-hour excretion of 17-ketosteroids was 30 mg. The patient was dis-

inclined to submit himself to the intravenous injection of histamine.

On the basis of the objectively studied attacks, and the lack of evidence of sustained hypertension, hyperthyroidism, polyglandular or Cushing's disease or brain tumor, the preoperative diagnosis of pheochromocytoma seemed justifiable. For three days preoperatively he was given a high salt diet with 4 Gm. of additional salt by mouth. Desoxycorticosterone, 5 mg., was administered intramuscularly the day before and the day of operation. Adrenal cortical extract, 5 cc., was given intramuscularly during the surgical procedure and was repeated immediately postoperatively.

Operation was performed on December 3, 1946, using a bilateral paravertebral approach to the adrenals; we had two surgical teams. Anesthesia used was tribromethylene rectally for induction, followed by intratracheal nitrous oxide and ether. A pheochromocytoma of the right adrenal gland was found that weighed 24.5 Gm. and had perforated the cortex, which was not greatly altered and was left *in situ*. The left adrenal was normal. Blood pressure fluctuations during the operation were controlled with injections of neosynephrine, epinephrine and epinephrine in oil; amyl nitrite inhalations were given without noticeable effect when the tumor was manipulated. The initial blood pressure was 180/100, and there was no period of alarming shock. When the tumor was handled, the systolic pressure rose to above 300 mm. mercury and the diastolic pressure was 260. Immediately after clamping the veins of the tumor pedicle the blood pressure dropped to 120/80. It then stabilized at 130/80 to 150/100. Adrenal hormonal therapy was not necessary postoperatively.

He has been seen as late as two years since his operation and reports no further attacks. His blood pressure is usually 130/70 when taken quietly at home but rises as high as 160/90 when he is examined in the office. He reports that he blushes at slight provocation since the tumor was removed whereas he had been previously untroubled in this way.

Comment. This patient suffered classical paroxysms of the "adrenal-sympathetic syndrome," and after excluding an intracranial cause for his violent headaches, by his own objective observations he was able to decide that he probably had a pheo-

chromocytoma. Completely negative results in an array of special laboratory and x-ray examinations substantiated his conclusion and justified the preoperative diagnosis on a purely clinical basis. He still has moderate vasomotor instability which has been noted in other cases.

COMMENT

Pheochromocytomas are being diagnosed preoperatively with increasing frequency. The importance of the diagnosis is greater now that the operative risk has been reduced by proper medical preparation and aid during the surgical and postsurgical periods and by added anesthetic and surgical experience. Hypertension, paroxysmal or sustained, caused by pheochromocytoma is promptly corrected by excision of the tumor; the effect is apparently lasting. The possibility of the presence of adrenal medullary tumor should be considered whenever the problem of hypertension is presented, and exploration of the adrenal glands should be part of every operation undertaken for the relief of hypertension. The use of new procedures such as the intravenous injection of histamine or the benzodioxane drugs may make the diagnosis simple and certain; experience with these tests is limited at present, and in cases of very high blood pressure they may be dangerous. Since all other tests, including x-rays, may be negative in the presence of pheochromocytoma, clinical observation remains the best guide.

SUMMARY

The clinical syndrome associated with tumors of the adrenal medulla (pheochromocytoma) is discussed with reference to the recorded experience in diagnosis and treatment. Three new cases at the Stanford University Hospital and Clinics in a two-year period are presented.

REFERENCES

1. MacKEITH, R. Adrenal-sympathetic syndrome; chromaffin tissue tumor with paroxysmal hypertension. *Brit. Heart J.*, 6: 1-12, 1944.
2. BELT, A. E. and POWELL, T. O. Clinical manifestations of the chromaffin cell tumors arising from the suprarenal medulla (suprarenal sympathetic syndrome). *Surg., Gynec., & Obst.*, 59: 9, 1934.
3. FRÄNKEL, F. Ein Fall von doppelseitigen, völlig latent verlaufenen Nebennierentumor und gleichzeitiger Nephritis mit Veränderungen am Circulationsapparat und Retinitis. *Virchow's Arch. f. path. Anat.*, 103: 244-263, 1886.
4. LABBÉ, M., TINEL et DOUMER, J. Crises solaire et hypertension paroxystique en rapport avec un tumeur surrenal. *Bull. et mém. Soc. méd. d' hôp. de Paris*, 46: 982-990, 1922.
5. VAQUEZ, H. and DONZELOT, E. Les crises d' hypertension artérielle paroxystique. *Presse méd.*, 34: 1329-1331, 1929.
6. PINCOFFS, M. C. A case of paroxysmal hypertension associated with suprarenal tumor. *Tr. A. Am. Physicians*, 44: 295-299, 1929.
7. BEER, E., KING, F. H. and PRINZMETAL, M., Pheochromocytoma with demonstration of pressor (adrenalin) substance in the blood pre-operatively during hypertensive crises. *Ann. Surg.*, 106: 85-91, 1937.
8. HOWARD, J. E. and BARKER, W. H. Paroxysmal hypertension and other clinical manifestations associated with benign chromaffin cell tumors (pheochromocytomata). *Bull. Johns Hopkins Hosp.*, 61: 371-410, 1937.
9. MCKENZIE, D. W. and McEACHERN, D. Adrenal pheochromocytoma: the syndrome of paroxysmal hypertension. *Tr. Am. A. Genito-Urin. Surgeons*, 31: 127-154, 1938.
10. NEFF, E. C., TICE, G. M., WALKER, G. A. and OCKERBLAD, N. Adrenal tumor in female infant. *J. Clin. Endocrinol.*, 2: 125-127, 1942.
11. STRÖMBECK, J. P. and HEDBERG, T. P. Tumor of the suprarenal medulla associated with paroxysmal hypertension. *Acta chir. Scandinav.*, 82: 177-189, 1939. BEER, E., KING, F. H. and PRINZMETAL, M. Pheochromocytoma with demonstration of pressor (adrenalin) substances in blood preoperatively during hypertensive crises. *Ann. Surg.*, 106: 85-91, 1937.
12. ROTH, G. M. and KVALE, W. F. A tentative test for pheochromocytoma. *Am. J. M. Sc.*, 210: 653-660, 1945.
13. ROTH, G. M. and KVALE, W. F. Ibid. MUNTZ, H. H., RITCHEY, J. O. and GATCH, W. D. Adrenalin producing tumor (pheochromocytoma) containing 2300 milligrams of adrenalin. *Ann. Int. Med.*, 26: 133-147, 1947. BURRAGE, W. C. Discussion Cabot Case No. 32511. *New England J. Med.*, 235: 910, 1946. BARTELS, E. C. and WALI, N. M. Clinical problem of pheochromocytoma. *S. Clin. North America*, 27: 605-615, 1947.
14. SNYDER, C. H. and VICK, E. H. Hypertension in children caused by pheochromocytoma. *Am. J. Dis. Child.*, 73: 581-601, 1947.
15. GOLDENBERG, M., SNYDER, C. H. and ARANOW, H., JR. New test for hypertension due to circulating epinephrine. *J. A. M. A.*, 135: 971-976, 1947.
16. FOURNEAU, E. and BOVET, D. Recherches sur l' action sympathicolytique d' un nouveau dérivé du dioxane. *Arch. internat. de pharmacodyn. et de thérap.*, 46: 178, 1933.

17. BISKIND, G. R., MEYER, M. A. and BEADNER, S. A. Adrenal medullary tumor; pheochromocytoma cured by surgical intervention; clinical management; analysis of all reported operated cases. *J. Clin. Endocrinol.*, 1: 113-123, 1941.
18. YOUNG, H. H. A technique for simultaneous exposure and operation on the adrenals. *Surg., Gynec., & Obst.*, 63: 179-188, 1936.
19. HYMAN, A. and MENCHER, W. H. Pheochromocytoma of the adrenal gland. *J. Urol.*, 49: 755-771, 1943. BRUNSWIG, A. Hypertension from pheochromocytoma. *J. A. M. A.*, 134: 253-255, 1947.
20. MUNTZ, H. H., RITCHEY, J. O. and GATCH, W. B. Adrenalin producing tumor (pheochromocytoma) containing 2,300 mg. of adrenalin. *Ann. Int. Med.*, 26: 133-147, 1947. GREEN, D. M. Pheochromocytoma and chronic hypertension. *J. A. M. A.*, 131: 1260-1265, 1946. CABOT CASE No. 32511. *New England J. Med.*, 235: 906-910, 1946. SNYDER, C. H. and VICK, E. H. Hypertension in children caused by pheochromocytoma; report of 3 cases and review of literature. *Am. J. Dis. Child.*, 73: 581-601, 1947. McCULLAGH, E. P. and ENGEL, W. J. Pheochromocytoma with hypermetabolism—two cases. *Ann. Surg.*, 116: 61-75, 1942.
21. GANEM, E. J. and CAHILL, G. F. Pheochromocytomas coexisting in adrenal gland and retroperitoneal space, with sustained hypertension. *New England J. Med.*, 238: 692-697, 1948.
22. GUARNERI, V. and EVANS, J. A. Pheochromocytoma, report of a case with a new diagnostic test. *Am. J. Med.*, 4: 806-813, 1948.
23. SPATT, S. D. and GRAYEL, D. M. Pheochromocytoma of the adrenal medulla. A clinicopathological study of five cases. *Am. J. M. Sc.*, 216: 39-51, 1948.
24. CAHILL, G. F. Pheochromocytomas. *J. A. M. A.*, 138: 180-187, 1948.
25. LADUE, J. S., MURISON, P. J. and PACK, G. T. The use of tetraethylammonium bromide as a diagnostic test for pheochromocytoma. *Ann. Int. Med.*, 29: 914-921, 1948.
26. SPEAR, H. C. and GRISWOLD, D. The use of dibenamine in pheochromocytoma. *New England J. Med.*, 239: 736-739, 1948.
27. GRIMSON, K. S., HENDRIX, J. P. and REARDON, M. J. Newer adrenolytic, sympatholytic, and ganglionic blocking drugs. *J. A. M. A.*, 139: 154-155, 1949.
28. DEVRIES, A., RACHMILEWITZ, M. and SCHUMERT, M. Pheochromocytoma with diabetes and hypertension. *Am. J. Med.*, 5: 51-59, 1949.

Treatment of Pernicious Anemia with Crystalline Vitamin B₁₂*

RANDOLPH WEST, M.D. and EDWARD H. REISNER, JR., M.D.

New York, New York

SINCE the initial publications recording the isolation from liver of crystalline vitamin B₁₂,¹ and a positive hematologic response² in Addisonian pernicious anemia following the injection of microgram doses, several confirmatory reports have appeared. These and the various steps leading to the discovery of B₁₂ have been summarized well in a recent editorial.³ E. L. Smith⁴ isolated similar crystals from liver, announced that they contained cobalt, nitrogen and phosphorus and suggested a molecular weight of 1,670 for the compound. Rickes et al.⁵ have found that vitamin B₁₂ contains these elements but no sulfur. Material with the same growth-promoting properties as B₁₂ has been isolated from other sources⁶ but the crystalline substance as yet has been recovered only from liver.

This paper reports eleven cases of Addisonian pernicious anemia treated parenterally with crystalline vitamin B₁₂, including the three original cases.² All have shown hematologic improvement, with blood counts rising to normal levels when weekly doses of 25 micrograms or less were injected. The minimal effective dose has been found to be 1 microgram a day, intramuscularly. Five patients with spinal cord lesions (Cases IV, VIII, IX, X and XI) have shown varying degrees of improvement; none has become worse, as has happened at times in treatment with pteroyl glutamic acid.⁷ All of these patients with spinal cord lesions are walking readily today. The effect of vitamin B₁₂ on the cord lesions of pernicious anemia appears promising but only a preliminary opinion can be given at this time. The

effective oral dosage of vitamin B₁₂ is being studied at other clinics.

Material Studied. All of the patients had classical Addisonian pernicious anemia with achlorhydria after histamine, a negative gastrointestinal x-ray, a typical blood picture and a megaloblastic bone marrow smear. All patients with spinal cord lesions had normal spinal fluids. While under study, the patients were on diets free from liver, kidneys or glandular meats and received no liver extract, folic acid or vitamin preparations.

CASE REPORTS

CASE I. A sixty-six year old female was admitted to Kings County Hospital because of progressive weakness, fatigability, anorexia and nausea of two months' duration. The positive physical findings on admission included pallor of the skin and mucous membranes, flame-shaped hemorrhages in the eye grounds and signs of mild congestive heart failure. The neurologic examination was normal. The blood count on admission was 1,500,000 with 4.00 Gm. of hemoglobin. Reticulocytes were 0.4 per cent. Five days after a single intramuscular injection of 0.15 mg. of vitamin B₁₂ there was a reticulocyte response of 27 per cent. The blood count rose steadily to 4,500,000 six weeks after this one injection. (Fig. 1.)

CASE II. A fifty-four year old male had noticed progressive weakness, pallor, dyspnea and precordial pain on exertion for one month prior to admission to the First Medical Division of Bellevue Hospital. The positive physical findings included pallor, lingual atrophy, slight enlargement of the heart with signs of mild congestive heart failure, a smooth liver enlarged 3 cm. below the rib margin, a palpable spleen tip and sluggish deep reflexes. There was no

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, and the Fourth Medical Division (New York University), Bellevue Hospital, New York.

impairment of vibratory or position sense. The admission blood count was 1,420,000 with 6.5 Gm. of hemoglobin. There were 2.8 per cent reticulocytes. Five days after a single intramuscular injection of 0.006 mg. of vitamin B₁₂ the reticulocytes reached a peak of 26 per cent.

to be weak and pale with a lemon colored hue to the skin, atrophy of the tongue, enlargement of the heart and liver and slight diminution of the vibratory sense below the knees. Position sense and deep tendon reflexes were normal. Her mental state was quite confused with alternating

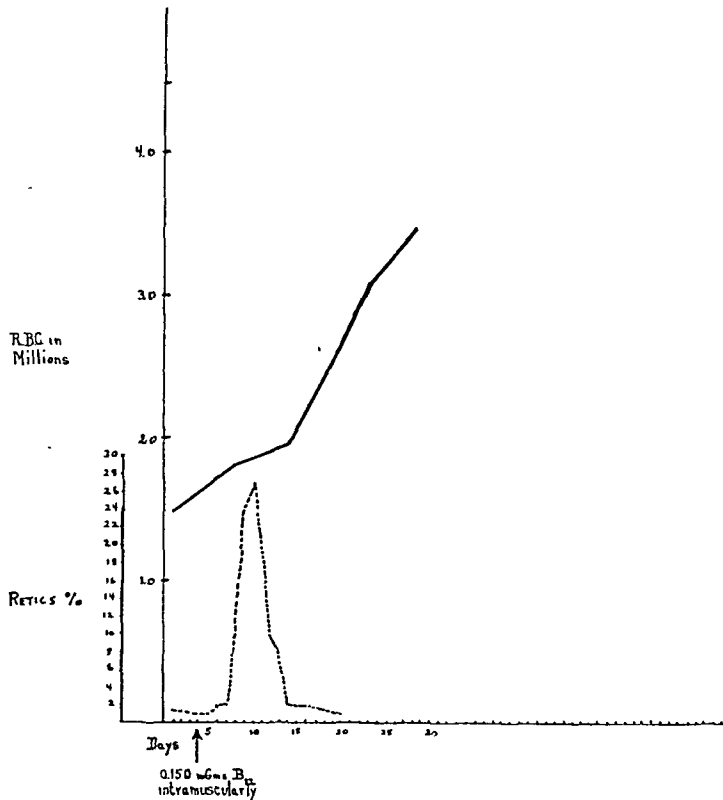


FIG. 1. CASE I. A sixty-six year old white female with pernicious anemia who had a maximal reticulocyte response of 27 per cent five days after a single injection of 0.150 mg. of vitamin B₁₂. She was transferred to another hospital where her count was reported to be over 4 million without any additional therapy.

A second injection of 0.50 mg. of B₁₂ was given two weeks after the first one. The red blood cell count was 4,750,000 sixty-four days after the start of treatment. Two months later it was still 4,500,000. (Fig. 2.)

CASE III. A sixty year old woman was admitted to the Fourth Medical Division of Bellevue Hospital in a semi-comatose, confused state. For twelve years she had been a semi-invalid and had taken various forms of non-specific anti-anemic therapy. For a month prior to admission she had been growing progressively weaker and had complained of soreness of the tongue and numbness of the fingers and toes. On the day before she entered the hospital she ate several pounds of liver because she was told it would help her. On admission she was found

periods of euphoria and paranoia. The blood count was 1,340,000 with 5.8 Gm. per cent of hemoglobin. There was a spontaneous rise of reticulocytes to 7.8 per cent four days after admission, attributed to the ingested liver. When the reticulocytes had dropped to 2.2 per cent, a single injection of 0.003 mg. of vitamin B₁₂ was given. This induced a reticulocyte rise to 10.4 per cent and rapid regeneration of red blood cells. Ten days later an injection of 0.05 mg. of B₁₂ was given. With no additional therapy, the blood count rose to 4,070,000 thirty-five days after the start of treatment. There was an accompanying gain of strength and appetite and less mental confusion but ideas of reference persisted and she was transferred to the psychiatric service. (Fig. 3.)

CASE IV. A sixty-nine year old laboring man had been admitted to the Fourth Medical Division of Bellevue Hospital on five previous occasions for hypertensive heart disease, chronic pulmonary tuberculosis, chronic alcoholism and, in 1947, pernicious anemia which re-

and the liver was palpable 3 cm. below the costal margin. There was absent vibratory sense in both forearms and legs and diminished sensation to pin-prick in the same areas. The deep reflexes in the lower extremities were diminished as was also the position sense in the toes. The blood

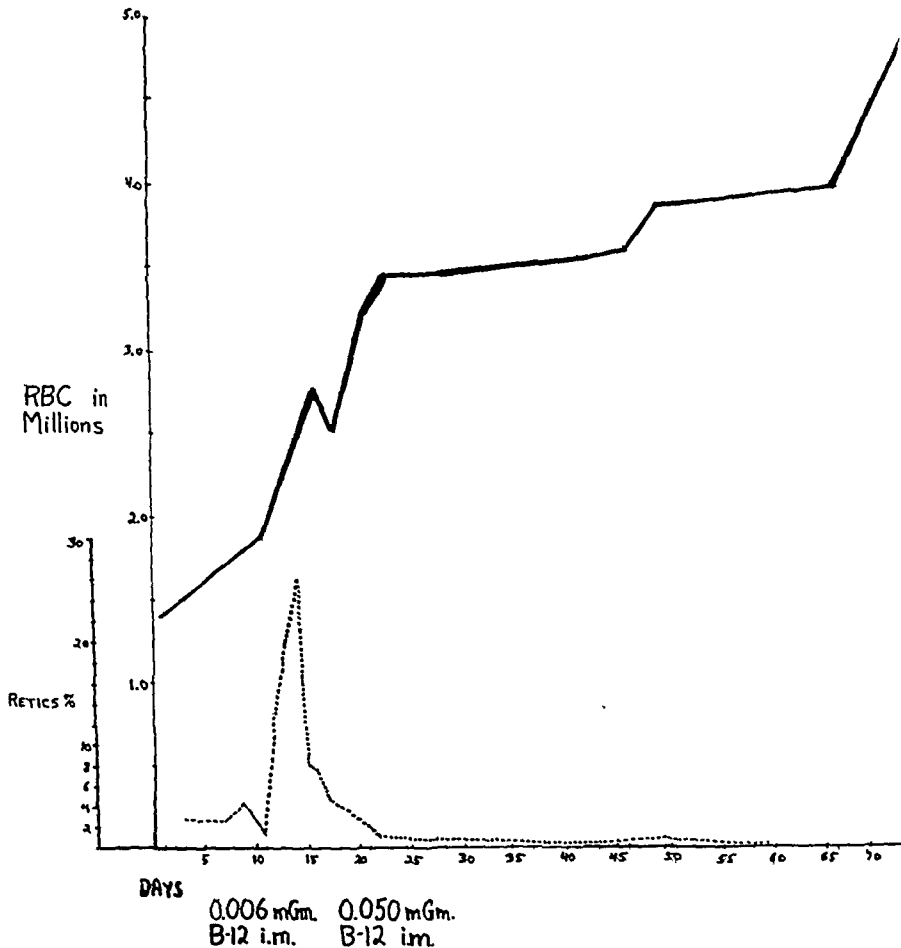


FIG. 2. Case II. A fifty-four year old white male with pernicious anemia who showed a maximal reticulocyte response of 26 per cent five days after a single injection of 0.006 mg. of vitamin B₁₂. A second injection of 0.050 mg. sent the blood count to 4,750,000 sixty-five days after the onset of therapy.

sponded to folic acid therapy with an 18 per cent reticulocyte rise. Following this admission he failed to continue therapy and gradually lost strength in early 1948. For a month prior to the present hospitalization he had a severe cough, anorexia, vomiting and dyspnea. For the last two weeks he had been too weak to leave his room and had subsisted mainly on coffee. On physical examination he was acutely and chronically ill, with a temperature of 101°F. There was dyspnea and orthopnea, pallor, lingual atrophy and pulmonary emphysema. Moist and crackling rales were heard in the left lower lobe. The heart was enlarged to the left

count on admission was 2,700,000 with 9.8 Gm. per cent of hemoglobin and 1.6 per cent reticulocytes. The chest x-ray revealed chronic fibroid phthisis with superimposed pneumonitis of the left lower lobe which gradually cleared under symptomatic treatment. Sputum culture was positive for tuberculosis. The patient was given a daily intramuscular injection of 0.001 mg. of vitamin B₁₂. On the ninth day of treatment the reticulocytes were 10.4 per cent. The blood count rose gradually and reached 4,470,000 after fifty-three days during which time there was rapid subjective improvement and relief of symptoms. Neurologic examination now showed

normal pin-prick, vibratory and position sense and active deep tendon reflexes. The patient was placed on liver extract and transferred to the tuberculosis service.

CASE V. A seventy-five year old woman with known pernicious anemia since 1937 was unable,

week of this dosage with no effect on the blood or reticulocyte levels the daily dose was increased to 0.0075 mg. A sub-maximal reticulocyte response of 7 per cent on the seventh day of this therapy was associated with extremely rapid regeneration of erythrocytes. (Table I.)

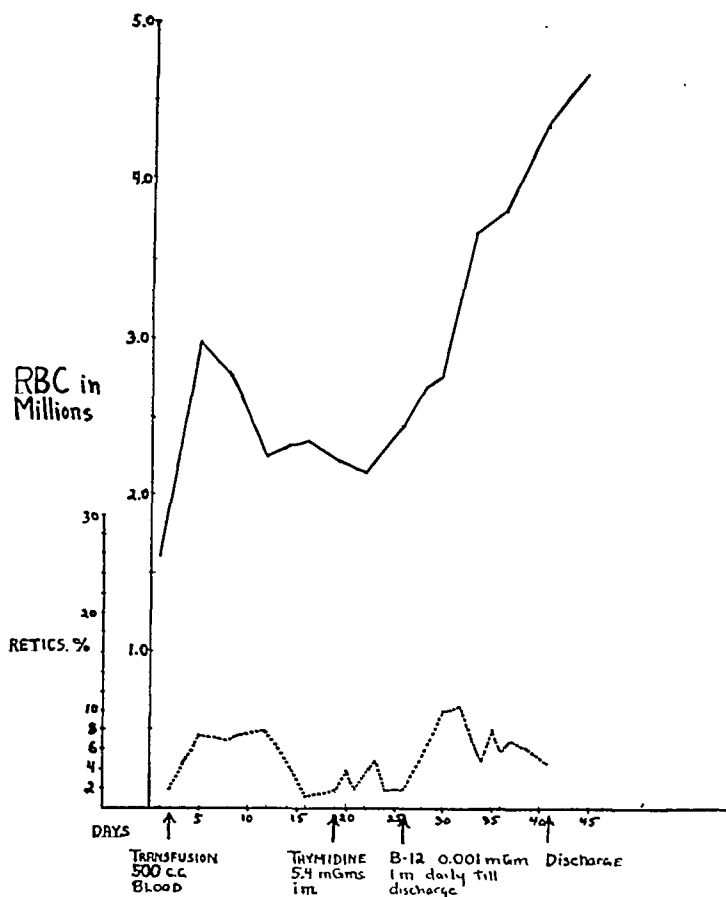


FIG. 3. Case VII. A fifty year old white female had pernicious anemia. Following a transfusion on admission, there was a spontaneous reticulocyte rise which persisted for two weeks. At this time she received 5.4 mg. of thymidine. One week later she was given 0.001 mg. of vitamin B₁₂ intramuscularly daily for fifteen days.

because of crippling arthritis, to come for liver injections and, therefore, was admitted to the Fourth Medical Division of Bellevue Hospital in relapse for the fourth time in June, 1948. On admission there was a marked glossitis, pallor of the skin and mucous membranes, dilatation of the heart, signs of mild congestive heart failure and extensive osteoarthritis. Except for a moderate diminution of vibratory sense below the knees, the neurologic examination was normal. The blood count was 1,810,000 with 8.5 Gm. per cent of hemoglobin and 0.8 per cent reticulocytes. Vitamin B₁₂ was started in daily intramuscular doses of 0.0001 mg. After a

After twenty-three days of this dose a single injection of 0.0125 mg. produced no further reticulocyte rise, indicating complete previous response. The blood count rose rapidly to 4,400,000 at which time the patient was discharged thirty-two days after beginning B₁₂ treatment on a dose of 0.0075 mg.

CASE VI. A forty-one year old man had noticed increasing weakness, anorexia and weight loss for six months. For six weeks he had noticed dyspnea and anginal pain on exertion and after meals. On admission to the Fourth Medical Division of Bellevue Hospital the positive physical findings included pallor and a

TABLE I
VITAMIN B₁₂ IN PERNICIOUS ANEMIA

Pa- tient, Hos- pital*	Sex	Age	Reticulo- cytes		Red Blood Cells (millions)														Type of Treatment Administered	
			Peak Per Cent	Day of Peak	At Start of Treat- ment	Day of Treatment														
						1	5	10	15	20	25	30	35	40	50	60	70+			
I-KC	F	66	27	5	1,5	...	1,8	1,9	2,6	...	3,3	0.150 mg. B ₁₂ i.m. ‡		
II-B	M	54	26	5	2,0	1,5	1,9	2,5	3,4	3,4	...	3,1	3,4	3,7	...	3,9	4,7	0.006 mg. B ₁₂ i.m. on 3/3/48 0.050 mg. on 3/16/48		
III-B	F	60	10.2	4	1,7	1,6	2,1	2,5	2,6	3,0	3,2	3,5	4,0	0.003 mg. B ₁₂ i.m. on 3/1/48 0.050 mg. on 3/10/48		
IV-B	M	69	10.4	9	2,4	2,4	2,7	2,9	3,2	3,4	3,5	...	3,9	3,8	4,4	0.001 mg. B ₁₂ i.m. daily for 47 days		
V-B	F	75	7	7	2,3	2,3	2,3	2,9	3,1	3,4	3,4	3,6	4,2	0.0001 mg. B ₁₂ i.m. daily 6/14/48-6/20/48 0.00075 mg. i.m. daily 6/21/48-7/8/48 0.0125 mg. in a single injection 7/14/48		
VI-B	M	41	13.4	8	1,3	1,3	1,5	1,9	2,3	2,2	2,5	2,9	3,3	4,5	0.0005 mg. B ₁₂ i.m. daily 6/21/48-7/12/48 0.0125 mg. B ₁₂ in a single injection 7/14/48		
VII-B	F	50	10.4	4	2,4	2,4	2,7	3,3	4,2	Transfusion 500 cc. 7/9/48 Thymidine 5.4 mg. i.m. 7/26/48 0.001 mg. B ₁₂ i.m. daily 8/2/48-8/17/48		
VIII-P	F	48	3,4	3,4	...	3,8	4,4	4,1	0.025 mg. B ₁₂ i.m. weekly from 7/21/48		
IX-P	F	50	29.1	5	1,6	1,6	...	3,0	3,6	3,7	...	3,9	5,1	...	5,7	0.150 mg. Co as CoCl ₂ i.m. 7/2/48 negative 0.025 mg. B ₁₂ i.m. weekly from 7/9/48		
X-P	M	57	14.0	8	3,3	3,3	...	3,9	4,1	...	3,7	3,7	...	4,7	...	0.025 mg. B ₁₂ i.m. weekly		
XI-P	M	44	9.2	6	2,5	2,5	4,3	4,6	5,2	0.010 mg. B ₁₂ then 0.025 mg. B ₁₂ i.m. weekly		

* KC = Kings County; B = Bellevue; P = Presbyterian.

† Or later.

‡ Intramuscularly.

lemon yellow hue to the skin, lingual atrophy, a systolic apical murmur in the heart and a liver edge palpable 3 cm. below the costal margin. Neurologic examination was normal. The blood count was 1,460,000 with 6.0 Gm. per cent of hemoglobin and 0.6 per cent reticulocytes. He was given a daily intramuscular injection of 0.0005 mg. of vitamin B₁₂ for twenty-one days. On the eighth day there was a sub-maximal reticulocyte response of 13.4 per cent. On the twenty-second day a single dose of 0.0125 mg. of B₁₂ was injected which was followed by a reticulocyte response of 10.4 per cent six days later. With no further treatment, the blood count reached 4,500,000 forty-six days after the beginning of therapy and the patient was discharged, free from symptoms.

CASE VII. A fifty year old white female with pernicious anemia diagnosed two years previously had taken liver injections until six months before admission. For the last two months there had been gradually increasing weakness and dyspnea. For four days she had had acute weakness, dyspnea, orthopnea and dependent edema. On admission to the Fourth Medical Division of Bellevue Hospital the patient was acutely ill with congestive heart failure. The heart was enlarged to the left with signs of mitral stenosis. The liver was palpable 8 cm. below the costal margin. Neurologic examination, done after the patient was compensated, was normal. The blood count on admission was 1,610,000 with 7.0 Gm. per cent of hemoglobin. She was given a transfusion of 500 cc. of whole blood on admission which brought about a spontaneous reticulocyte rise up to 8 per cent. The heart failure was treated with oxygen, digitoxin and mercurial diuretics and no specific anti-anemic therapy was given until eighteen days after admission. At this time her blood count was 2,210,000 and reticulocytes were 2.0 per cent. An intramuscular injection of 5.4 mg. of thymidine was given without significant effect on the blood picture. On the twenty-sixth hospital day daily injections of 0.001 mg. of B₁₂ were begun. There was a prompt reticulocyte rise to 10.6 per cent five days later. The red blood cell count rose remarkably rapidly and reached 4,550,000 eighteen days after the start of B₁₂ therapy. There was complete relief of symptoms of heart failure at this time and the patient was discharged.

CASE VIII. A forty-eight year old woman had

parasthesias of the extremities for three years and difficulty in walking for one year prior to admission to Presbyterian Hospital. For the last year she had amenorrhea. Positive physical findings on admission were limited to the neurologic system. There was diminished vibratory and tactile sensation in the hands and feet, positive Romberg, staggering gait, hyperactive deep reflexes and normal plantar reflex. The red blood count was 3,600,000 with 12.0 Gm. of hemoglobin. She was given 0.025 mg. of vitamin B₁₂ every week for three months. The blood picture was restored to normal in a month and there was rapid return of strength and subjective improvement. At the end of five months of treatment neurologic examination revealed marked improvement in the Romberg test, definite improvement in gait and no change in the vibratory sense.

CASE IX. A fifty year old housewife, who had suffered from soreness of the tongue and weakness and numbness of the legs for two months, was admitted to Presbyterian Hospital. Physical examination disclosed marked pallor, atrophy and inflammation of the tongue and vitiligo. Vibratory sense was absent below the knees, position sense was absent in the toes, reflexes were normal, there was no Babinski reflex and the Romberg test was slightly positive. Initial red blood cell count was 1,600,000 with 6.5 Gm. of hemoglobin; 150 micrograms of cobaltous ion (as chloride) was given intramuscularly with no hematologic response. A reticulocyte count of 29.1 per cent was recorded five days after an injection of .025 mg. of vitamin B₁₂. Thereafter, she received a similar dose of B₁₂ weekly. The blood picture returned to normal at the end of six weeks and there was accompanying subjective improvement. After four months the Romberg test was negative; position sense was improved but vibratory sense was still diminished to absent in the lower extremities.

CASE X. A fifty-seven year old white man had been treated for pernicious anemia for three years. During the first two years he was treated by a doctor with both liver extract injections and oral folic acid. For the last year the patient had treated himself with folic acid, taking about 3,000 mg. by mouth in that time. Two weeks before his admission to Presbyterian Hospital he noticed paresthesias of the hands and feet and an unsteady gait. The positive physical findings were absent vibratory and position sense in the lower extremities, normal

Babinski, deep tendon reflexes and a markedly positive Romberg. The red blood count was 3,300,000 with 11.0 Gm. of hemoglobin. There was an excellent hematologic response to .025 mg. weekly of vitamin B₁₂ with accompanying clinical improvement. (Table 1.) After 3 months of treatment the Romberg test was questionably positive and there was marked improvement of gait but vibratory sense was still absent below the knees.

CASE XI. A forty-four year old white male had complained of impotence, leg paresthesias and difficulty in walking for six months. Recently he had noticed clumsiness and numbness of the hands. Four days before admission to Presbyterian Hospital he developed a productive cough and fever. On admission he was acutely ill with signs of consolidation of the left lower lobe. The neurologic examination showed a strongly positive Romberg, absent vibratory sense in the lower extremities and a Babinski reflex on the right side. The initial blood count showed 2,500,000 erythrocytes, 8.5 Gm. of hemoglobin and 9,000 leukocytes. The sputum contained *Streptococcus viridans* and *Hemophilus influenzae*. After two weeks of penicillin therapy his temperature returned to normal. He was given an initial dose of 0.010 mg. of vitamin B₁₂ and .025 mgs. weekly thereafter. The blood count returned to normal rapidly. (Table 1.) After seven months the Romberg test was slightly positive, there was no Babinski reflex and vibratory sense was still absent from the lower extremities. When last seen the patient's gait was steady and he felt well.

COMMENTS

The discovery of cobalt in vitamin B₁₂ is of great interest because that element had previously been implicated in hematopoiesis. The available literature on this subject has been summarized by several authors.^{8,9} The salts of the metal alone given to one of our patients (Case ix) were without effect. Studies with salts of radioactive cobalt have shown that after parenteral injection they are recoverable in part in the stomach contents of cattle¹⁰ and are stored in greatest concentration in the liver, pancreas and kidneys, respectively. Cobalt must enter the body from without, but there is no parallelism between the cobalt content of

foods and their content of extrinsic factor, as shown in a study by Morris.¹¹

The question will be raised at once where B₁₂ fits into our present knowledge of hematopoiesis and what relationship it bears to two other crystalline substances with anti-pernicious anemia activity, thymine¹² and pteroyl-glutamic acid.¹³

Thymine can replace folic acid in the growth requirements of certain bacteria in a ratio of 3,000:1.¹⁴ Thymine in the same high proportions (12 to 15 Gm. per day) will maintain patients with pernicious anemia in hematologic remission but, like folic acid, it has no favorable effect on the cord lesions of that disease.¹⁵ From this it appears that folic acid may act as a coenzyme in the metabolism of thymine. Wright et al.¹⁶ have reported that thymidine (thymine desoxyriboside) in comparatively high concentrations can replace vitamin B₁₂ in the growth of *Lactobacillus lactis* and conclude that vitamin B₁₂ may function as a coenzyme in the conversion of thymine to thymidine. Thymidine (5.4 mg.) given to the patient in Case vii produced a rise in reticulocytes from 2.0 to 5 per cent but caused no significant change in the blood level. With the subsequent administration of 1 microgram a day of vitamin B₁₂, the blood count returned to normal in fifteen days.

CONCLUSIONS AND SUMMARY

1. Eleven patients with Addisonian pernicious anemia have been treated with crystalline vitamin B₁₂. All have shown complete hematologic remission. Five patients with combined system disease have shown marked improvement in their neurologic condition.

2. The effective parenteral dose has been found to be slightly less than 1 microgram of crystalline vitamin B₁₂ a day.

3. The current status of our knowledge of the relationship of thymine, folic acid, cobalt and vitamin B₁₂ is discussed.

4. It would appear that vitamin B₁₂ is probably the erythrocyte maturation factor of liver.

We wish to express appreciation to Dr. William Dock, Professor of Medicine, Long Island College School of Medicine, for permitting the inclusion of Case I and to Dr. William Bauman who supplied the protocol. Thanks also are due to Dr. Dickinson Richards, Director of the First Medical Division, Bellevue Hospital, for Case II and to Dr. Amanda Hoff who supplied the protocol.

REFERENCES

1. RICKES, E. L., BRINK, N. G., KONIUSZY, F. R., WOOD, R. R. and FOLKERS, K. Crystalline vitamin B₁₂. *Science*, 107: 396, 1948.
2. WEST, RANDOLPH. Treatment of pernicious anemia with vitamin B₁₂. *Ibid*, 107: 398, 1948.
3. Editorial. Antianemic properties of vitamin B₁₂. *J. A. M. A.*, 138: 595, 23, 1948.
4. SMITH, E. LESTER. Presence of cobalt in the anti-pernicious anemia factor. *Nature, London*, 162: 144, 1948.
5. RICKES, E. L., BRINK, N. G., KONIUSZY, F. R., WOOD, T. R. and FOLKERS, K. Vitamin B₁₂ a cobalt complex. *Science*, 108: 134, 1948.
6. SHORB, Mary S. Activity of B₁₂ for the growth of *Lactobacillus lactis*. *Science*, 107: 397, 1948.
7. ROSS, J. F., BELDING, H. and PAEGEL, B. L. The development and progression of subacute combined degeneration of the spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid. *Blood*, 3: 68, 1948.
8. SHILS, M. E. and MCCOLLUM E. V. The trace elements in nutrition. *J. A. M. A.*, 120: 609, 1942.
9. CARTWRIGHT, G. E. Dietary factors concerned in erythropoiesis. *Blood*, 2: 111-153, 256-298, 1947.
10. COMAR, C. L., DAVIS, G. K. and TAYLOR, R. F. Cobalt metabolism studies: radioactive cobalt procedures with rats and cattle. *Arch. Biochem.*, 9: 149, 1946.
11. MORRIS, J. P. Cobalt content of some tropical foods. *J. Malaya Br., Brit. M. A.*, 4: 279, 1940.
12. FROMMEYER, W. B., JR., SPIES, T. D., VILTER, C. F. and ENGLISH, A. Further observations on anti-anemic properties of 5-methyl uracil (thymine). *J. Lab. & Clin. Med.*, 31: 643, 1946.
13. MOORE, C. V., BIERBAUM, O. S., WELCH, A. D. and WRIGHT, L. D. Activity of synthetic *Lactobacillus casei* factor (folic acid) as anti-pernicious anemia substance. *Ibid*, 30: 1056, 1945.
14. STOKES, J. L. Substitution of thymine for folic acid in the nutrition of lactic acid bacteria. *J. Bact.*, 47: 433, 1944.
15. SPIES, T. D. and STONE, R. E. Liver extract, folic acid and thymine in pernicious anemia and subacute combined degeneration. *Lancet*, 1: 174, 1947.
16. WRIGHT, L. D., SKEGGS, H. R. and HULF, J. W. The ability of thymidine to replace vitamin B₁₂ as a growth factor for certain *Lactobacilli*. *J. Biol. Chem.*, 175: 475, 1948.

Seminars on Congestive Failure

Cardiac Venous Congestion*

Its Causes and Consequences

JOHN McMICHAEL, M.D., F.R.C.P.

London, England

"If then, Socrates, we find ourselves in many points unable to make our discourse . . . in every way wholly consistent and exact, you must not be surprised. Nay, we must be well content if we can provide an account not less likely than another's."

Plato, "The Timaeus"—A. E. Taylor's Translation

THE straightforward idea that blood is dammed up in the veins behind a failing heart and that, in consequence, fluid leaks from the capillaries under pressure has an attractive simplicity. The vital machinery of the body, however, is much more complex, and this simple view is no longer adequate to explain all the observable phenomena.

There is a good deal of loose thinking concerning the way in which an increase or a decrease in cardiac output reacts on the venous pressure. It is commonly remarked that when the cardiac output increases the venous pressure falls, as though the blood were lifted out of the venous system and transferred into the arteries. It is clear, however, that the rate of removal of blood from the central end of the veins must equal the rate of inflow into the veins at the peripheral end. The volume of blood within the veins will thus remain unchanged. There is no fundamental reason, therefore, why an increased minute volume of the circulation should make any difference to the general venous pressure unless the capacity of the venous system is changed by some alteration in tone of the vein walls.

The pressure gradient in the veins, however, may alter with an increase in cardiac output, a higher pressure occurring at the peripheral end of the venous system and a lower pressure at the centre. In heart failure, with decreasing blood flow, diminution of the pressure difference between

peripheral and central veins is a natural consequence.^{25, 48} Numerous instances can be quoted in which acutely produced changes in cardiac output are not accompanied by simple consequential changes in the central venous pressure. The following may be cited as examples: (1) Adrenaline has been shown to increase the cardiac output in normal man without significant change of venous filling pressure.³⁷ (2) Venous pressure changes induced experimentally usually influence the cardiac output in a parallel direction, i.e., a rise in venous pressure causes a rise in output, while the converse result occurs when the venous pressure is reduced (Starling's Law).^{28, 37, 45}

It is therefore not justifiable to assume that increased minute volume of the circulation is necessarily accompanied by a passive fall in venous pressure. Should the venous pressure fall be primary, the cardiac output may well be reduced.

As a result of studies on cardiac output with the technique of cardiac catheterization it is now widely realized and accepted that the rise of venous pressure in heart failure is not a simple direct mechanical consequence of a low heart output at rest.^{33, 35, 46, 61} In the early stages of congestive heart failure the output of the heart is often within normal limits when the venous pressure is raised.^{33, 61} A large group of patients (emphysema, anemia, beri-beri, etc.) may present the phenomena of venous

* From the Department of Medicine, Postgraduate Medical School of London, London, England.

engorgement and accompanying oedema and yet have a high cardiac output.^{35,46,61} In such patients the raised venous pressure cannot be the result of inadequate pumping of blood by the heart.

We are thus compelled to reconsider the whole problem of cardiac venous congestion along new lines. We have briefly mentioned the way in which change of cardiac output and blood flow may affect the gradient of venous pressure, and further consideration of the influence of a failing heart on the venous pressure will be outlined below.

The major factors influencing venous pressure are: (1) the tone of the vein walls and (2) the volume of blood within the veins. Of these the first is probably the more important physiologically, as it is more adaptable to rapid adjustment.

VENOMOTOR REGULATION*

The venous system can no longer be considered as a system of passive tubes leading blood back to the heart. It is a matter of common clinical experience to observe the contractile character of the veins. We have all made use of the tapping process in order to dilate a contracted vein, the so-called "Klopfversuch" of Goltz.¹⁸ Similarly, in the terminal stages of heart failure, when the central veins in the neighbourhood of the heart are grossly engorged, everyone has had the experience of inability to find an arm vein sufficiently large for insertion of a needle.

In 1890 Roy and Sherrington⁵¹ showed that "there are in the vago-sympathetic nerves descending fibres, section or stimulation of which can produce either a rise or a fall of the general venous pressure." Donegan¹¹ observed contraction of the veins of the legs in response to stimulation of the sciatic nerve. This contraction was apparently mediated by the sympathetic fibres

carried in the nerve. In man, Lewis and Landis²⁹ observed dilatation of the veins of the arm and hand following sympathectomy, and this relaxation of the vein walls was shown to be independent of the local temperature. There is good evidence that these venomotor nerves are connected to a regulating centre closely associated with the other vasomotor regions in the central nervous system. Doupe, Krynauw and Snodgrass¹² were able to demonstrate constriction of an isolated section of an arm vein in man during exposure of the rest of the body to cold. Fleisch¹⁴ and Gollwitzer-Meier and Bohn¹⁷ showed that the inhalation of carbon dioxide brought about contraction of an isolated segment of vein with intact nervous connections but not exposed to the change in blood-gas content. Fleisch¹⁵ was also able to demonstrate that a rise in pressure in the carotid sinus produced dilatation of the veins of the mesentery, while Charlier and Philippot⁶ have recently demonstrated that reduction of pressure in the carotid sinus is accompanied by a rise in pressure in the right auricle with an increase in cardiac output in the dog.

An observation by Riml⁴⁹ is also of interest. When the pulmonary artery of a rabbit is tied and the cardiac drive to the circulation ceases, half the animal's blood volume may flow out of the veins near the heart when these are incised; prior to incision the pressure rises steeply. In the absence of any systolic ejection into the arteries, this rise of pressure in the venous system can only result from contraction of the veins and venules. This is probably another illustration of increased venomotor tone resulting from cutting off the cerebral blood supply.

These examples make it clear that the tone of the muscular walls of the veins is subject to venomotor regulation. The general rule which seems to underlie the venomotor reflexes in the data given above is that a rise of venous pressure occurs when there is need for a greater cerebral circulation and, conversely, a dilatation of the

* In this brief account of venous pressure regulation the influence of such mechanical factors as limb muscle movements and respiratory variations is omitted. These influences are of a transient nature and cannot play any part in the production of the sustained rise in venous pressure in heart failure.

veins and fall in venous pressure results when the pressure in the carotid artery is high, while the opposite occurs when the pressure is reduced. In these particular instances it would appear that the rise or fall of venous pressure may influence cardiac output in an appropriate direction, greater cardiac output being brought about when this is needed.

STARLING'S LAW OF THE HEART

The direct relationship between venous pressure and cardiac output (Starling's Law), implicit in the above remarks on venous pressure regulation, requires some further elaboration.

The principle established by Starling and his collaborators⁴⁰ was that the strength and magnitude of systolic ejection (stroke output) is dependent upon the length of the cardiac fibres in diastole. Although there was a general relationship between the filling pressure of the right auricle and cardiac output, Starling himself did not think that the diastolic fibre length was solely determined by the pressure within the ventricle at the end of diastole. His methods, however, were probably not adequate; and when Wiggers⁶⁷ re-studied the problem later, it was found that the diastolic filling pressure was, in fact, the decisive factor.

Starling's Law was, of course, worked out on isolated hearts freed from other influences, nervous and hormonal. The direct relationship between venous filling pressure and cardiac output has often been demonstrated in man.^{28,37,45} Bleeding to a sufficient degree may reduce the cardiac output considerably while saline infusions may increase it.³⁷ The stroke output has been shown to vary with the "net filling pressure" accompanying the changes of the respiratory cycle.⁴⁵ Sometimes, however, the expected relationship between cardiac output and filling pressure may not be demonstrable in intact man.⁶⁴ This is scarcely surprising as the presence of other nervous and humoral controlling influences may make

the maintenance of standard conditions of cardiac contractility impossible.

While there is considerable unanimity of opinion that the cardiac output is reduced when the diastolic filling pressure is low in various conditions of "shock,"⁴⁵ it is not at all clearly established that a rise in venous pressure is a primary factor in determining increased cardiac output under physiologic stress. In exercise, for example, it seems to be well established that the venous pressure may not rise much⁶³ and may even fall²⁷ while the heart may not enlarge significantly until the exercise becomes severe.³⁰ Thus the first mechanisms which bring about an increased cardiac output in health are probably cardio-acceleration and increased emptying of residual blood from the ventricles.³⁰ There is now strong evidence that the ventricles do in fact contain blood at the end of a normal contraction. This has been demonstrated by a discrepancy between the heart volume and stroke output.^{31,32} Lysholm and his collaborators found the average heart volume in normal recumbent subjects to be 630 cc. If we take a stroke output of 80 cc. from each ventricle, the heart volume at the end of systole will be $630 - 160$, i.e., 470 cc. As the specific gravity of heart muscle is slightly greater than unity, the volume of the heart muscle is unlikely to exceed 300 cc. in a heart of normal weight. This leaves a residual blood of 170 cc. which is probably more than can be accounted for in the auricles. Cournand⁹ has observed that a premature beat may eject blood even though the premature contraction begins when the pressure in the ventricle is still too high for blood to have flowed in from the auricles.

It has been shown³⁰ that the heart volume in healthy young men may scarcely increase at all with moderate work while heavy work produces, on the average, a 12.7 per cent enlargement. Immediately after exercise the heart volume usually decreases below the control value. It is highly probable therefore that the venopressor mechanism for increasing cardiac output by elongation

of the myocardial fibres only comes into action in severe physical effort while in the earlier stages of work the cardiac output is increased by other mechanisms—nervous and humoral.

When the heart is “decompensated,” however, a sustained and considerable rise in venous pressure takes place in exercise which persists after exercise is over.⁵³ This is in contrast with the slight rise followed immediately afterward by a fall occurring in normal healthy subjects.⁶³ A raised venous pressure occurs in patients with severe anemia in whom the cardiac output is high at rest.⁵⁴ Although this raised venous pressure may be regarded as “compensatory,” it must, in fact, be the last resource of the compensating mechanisms, for a further rise in venous pressure in such patients is likely to induce a *fall* in cardiac output⁵⁶ together with pulmonary congestion and various signs of heart failure. It is clear then that anemic hearts compensated in this manner are, in fact, on the very brink of failure which may readily be precipitated by slight further increases in venous filling pressure.

Venopressor adjustments are therefore to be regarded as subsidiary mechanisms in health, coming into action only in the later stages of severe muscular effort. They come into action more readily in heart disease but their development is an indication of the imminence of heart failure.

RISE OF VENOUS PRESSURE IN CARDIAC FAILURE

Experimental. Starr and his co-workers⁵⁹ have produced severe damage to the right ventricle by burning in dogs without any consequent rise of venous pressure. Roos and Smith⁵⁰ showed that it was possible to get some rise in venous pressure by embolization of the coronary arteries with starch granules. Very severe diffuse embolization, however, was necessary and unfortunately no observations on change in cardiac output were made. The venous pressure rises achieved were modest, ranging from 1.5 to 3 cm. of water. Landis and his collaborators²⁷ have also produced impairment of

myocardial capacity for work by ligating coronary arteries and by experimental auricular fibrillation. Neither of these methods leads to a rise in venous pressure at rest. Prinzmetal⁴² has also noted the absence of venous congestion as a result of extensive coronary ligation. When animals with these impaired hearts, however, are subjected to exercise, the venous pressure rises. This was in contrast with the fall in venous pressure which occurs normally in exercise.²⁷ In animals with pericardial tamponade the raised venous pressure was found to fall somewhat in exercise, but this was an inconstant result, and in one example in the paper by Landis et al.²⁷ the increased arterial pulse pressure suggested that the cardiac output did, in fact, increase during the exercise. Inability to increase cardiac output adequately during exercise is probably an early mechanism inducing a rise in venous pressure. (Fig. 1.)

Clinical. In the introductory section reasons were given for discarding the old view that blood is simply dammed up behind the failing chamber, the most cogent of which was the observation that all the phenomena of heart failure may appear with an output raised above the normal.

Among the explanations offered to account for raised venous pressure in heart failure is an increase in blood volume. There is a considerable body of evidence that the blood volume is increased;¹⁶ and in spite of criticisms concerning the validity of the dye method⁴¹ in the presence of large volumes of oedema fluid into which leakage of the dye may take place, the evidence must be accepted as adequate. It has frequently been observed that some concentration of the blood takes place during recovery from cardiac failure.⁶⁹ Landis and his group, however, have shown that an increased blood volume is by itself inadequate to maintain a raised venous pressure in animals in which the circulation is otherwise normal.²⁷ In the presence of heart failure, however, saline infusion will produce a maintained rise in venous pressure,⁴⁷ a finding in contrast with the rapid

restoration of venous pressure toward normal in otherwise healthy subjects. It seems unlikely then that a raised blood volume is an important primary event in raising venous pressure but its secondary development in the presence of a failing heart

in response to tissue needs at a higher level of cardiac output.⁶¹ The venopressor reaction may be induced, perhaps, by local metabolic changes of an "asphyxial" character in the venomotor centre.

The manner in which the venous pressure

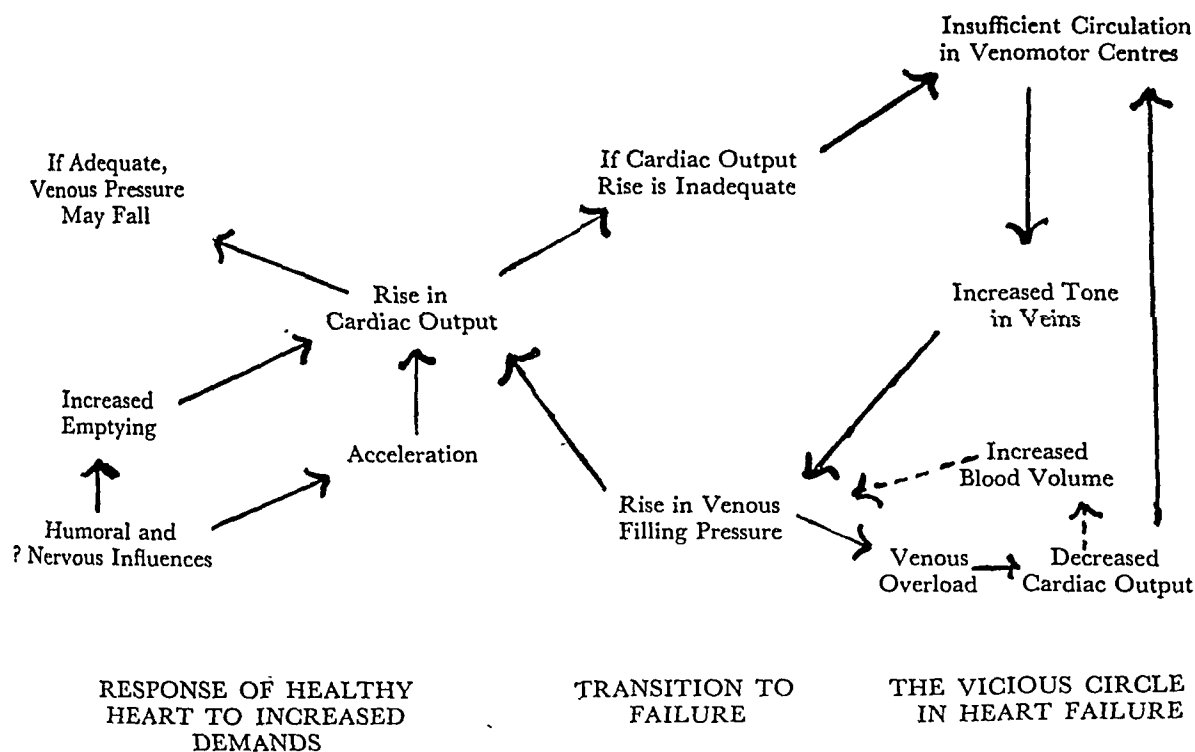


FIG. 1.

may play some part in sustaining venous congestion.

There are numerous instances, however, in which a raised venous pressure may develop so rapidly that increased blood volume cannot be invoked to account for it. An example of this occurs in traumatic pericardial haemorrhage.⁶⁶ Here there is probably a reduced blood volume but the venous pressure is raised to a level adequate to maintain filling of the heart against the external pressure exerted by the effused blood. Similarly, there is evidence that the blood volume in some cases of severe anemia is reduced, but in spite of this the venous pressure is often raised.⁵⁴ In the absence of a blood volume increase as an initiating mechanism we must postulate the intervention of a venopressor adjustment. In "high output" failure the venopressor mechanism is probably brought into action

first rises in failure accompanying valvular hypertensive and ischemic heart disease (low output group) is a matter still somewhat difficult to analyze. Perhaps the clue is to be found in studies of the reaction to exercise. It was found by Schott⁵³ that exercise was accompanied by a gross and prolonged rise in venous pressure in cardiac patients. This contrasts with normal subjects in whom the venous pressure rises only slightly during the muscular movements, falling below normal immediately the exercise is over.⁶³ Hickam and Cargill²⁰ have shown that the cardiac output often fails to rise or may even fall during exercise in cardiac patients when the systemic venous pressure is considerably raised above the pre-exercise level. It would appear, therefore, that a venopressor reaction in response to an inadequate cardiac output during exercise can be regarded as one important

way in which the venous pressure is raised. The well known beneficial value of complete bed rest in the early stages of cardiac failure fits very well with the concept that effort and exercise are important in initiating venous congestion.

Once the venopressor mechanisms are brought into action by an inadequate circulation they may at first play a part in maintaining compensation. This is, perhaps, best seen in the high output group in which lowering of the venous pressure may be accompanied by a decrease in a desirably high cardiac output. A further rise in venous pressure, however, is likely to be harmful,⁵⁶ depressing the cardiac output below the optimum level in the manner demonstrated by Starling when he overloaded the isolated heart.²³

In the low output group the clearest evidence of the overloading effect of a raised venous pressure is obtained by observing the influence of a venesection.²³ In practically every instance simple mechanical reduction of venous pressure so induced leads to an increase in the cardiac output with an increase in the external work of the heart of some 20 to 40 per cent.²³ Conversely, the danger of transfusions in patients with heart failure is well known. In Hickam and Cargill's observations of the fall in cardiac output with the raised venous pressure of exercise it is possible to apply the interpretation that the heart had been subjected to a mechanical venous overload.

This pathologic reversal of the normal relationship between venous filling pressure and cardiac output may bring about a vicious circle in heart failure; the raised pressure tends to keep the output down while the low output will keep the venopressor mechanism in action. (Fig. 1.) In the early stages venesection is beneficial. Patients themselves have found how to induce relief by adopting the upright position, a measure which reduces the pressure in the right auricle, particularly in paroxysmal nocturnal attacks of failure.

INTERPRETATION OF CHANGES IN CARDIAC OUTPUT AND VENOUS PRESSURE IN HEART FAILURE

The importance of venomotor mechanisms adaptable to the circulatory conditions has been emphasized. The possibility has to be kept in mind that certain pharmacologic substances may have important influences on the venous pressure with secondary consequences on the cardiac output. When therapeutic measures in heart failure lead to a rise in cardiac output and a fall in venous pressure, there are two alternative explanations: (1) Evidence is abundant that in low output heart failure a primary reduction of venous pressure such as that brought about by venesection will lead to an increase in cardiac output.^{23,46,62} (2) When the circulation has been inadequate and the venous pressure is raised in consequence, a primary change in the heart itself leading to increased output may have as a result a diminution of venomotor tone and a fall in venous pressure. The interpretation of the mode of action of certain drugs used in treatment remains a matter of some difficulty in consequence of these two alternatives.

It has been shown that mersalyl reduces the venous pressure and raises the cardiac output during mercurial diuresis.^{34,43} There is no pharmacologic evidence to suggest that mercurials have a primary action on cardiac contractility and the most reasonable interpretation is therefore a venesection-like action resulting from blood volume reduction at the peak of the diuresis.

Theophylline also lowers the venous pressure within a few minutes of injection and this is accompanied by a very considerable rise in cardiac output²¹ particularly in hypertensive cardiac failure. The rise in output has been found to be considerably greater than would be expected from simple mechanical reduction of venous pressure, and this action is therefore interpreted as being mainly the result of an adrenaline-like stimulation of cardiac contraction.

The actions of the digitalis series have been much more difficult to interpret on the evidence obtained from clinical experiment.^{3, 23, 36, 60} Venous pressure and cardiac output effects are quantitatively similar after digoxin and venesection.²³ There is a considerable consensus that digitalis has a slight but consistent primary venous pressure lowering action in normal animals and man,^{5, 10, 24, 52, 70} and this action has been regarded as responsible for the fall in cardiac output which takes place when digitalis is given to normal animals and man.³⁶ From what has already been said about venesection such a venous pressure reducing action might well play a part in producing the cardiac output improvement which follows the administration of digitalis to many patients with low output heart failure.

Further work with ouabain,^{3, 34} however, shows that the stimulating action of this glycoside on cardiac contractility in the failing human heart is very striking, and in many instances a rise in output precedes significant venous pressure reduction. A similar stimulating action of digoxin, though presumably present, has been much more difficult to demonstrate by clinical experiment. There are many instances in which digoxin appears to have brought about a fall in venous pressure with no significant change or even with a reduction in cardiac output.^{22, 60} It cannot, therefore, be claimed that the venous pressure falls as a simple secondary consequence of an increasing cardiac output. Quite a small initial fall in venous pressure induced by digoxin in favourable circumstances may induce a cardiac output rise and break the vicious circle of cardiac failure. It is difficult to escape the conclusion that there are two separate actions of the digitalis series which influence cardiac contractility: one is the stimulating action seen in certain types of failing myocardium and which is particularly well seen with ouabain; the other is a venous pressure reducing action, more strikingly seen with digoxin than with ouabain.

There are instances in which both venous pressure and cardiac output seem to be completely refractory to the cardiac glycosides.⁶⁸ The significance of this group is not at all clear. It includes instances of anemic heart failure and cases in which the venous pressure has been artificially raised by salt and D.C.A. Wood⁶⁸ suggests that these cases may not be in true heart failure, but similar refractoriness may be seen in advanced heart failure and in aortic valve disease particularly. Sometimes the venous pressure reducing action of digitalis may be apparently offset by a pronounced effect of the drug in raising the arterial pressure.⁷⁰

LEFT HEART FAILURE

When the left ventricle fails primarily, a stage may be seen in which venous engorgement affects the pulmonary vessels only while the systemic venous pressure may not be raised outside normal limits. In this state of affairs it seems probable that pulmonary venous engorgement is brought about by an initial lack of balance between right and left heart output. The imbalance can continue only until the pulmonary veins are sufficiently engorged and the pressure within them becomes high enough to drive the left heart to put out a volume of blood equal to that of the right. Pulmonary engorgement is a necessary accompaniment and leads in the first instance to a diminished vital capacity and later to lung oedema. The engorgement of the lung vessels is a major factor in the production of dyspnoea (difficult breathing).⁷

The rise of pulmonary venous and capillary pressure may be responsible for the rise in pulmonary arterial pressure¹⁹ recorded by Bloomfield and others² and by Hickam and Cargill²⁰ in left heart failure. This pulmonary arterial pressure rise is reduced by digoxin⁹ and is apparently elevated by ouabain,³ which is a further interesting point of difference in the action of these two glycosides.

Attacks of acute left ventricular failure are accompanied by further elevation of the arterial pressure, the so-called "Hoch-

druckstauung" of the Germans. Whether this is the cause or consequence of the attacks of failure is not yet clearly defined.

TRICUSPID INCOMPETENCE

The venous pressure change which takes place as a result of relative insufficiency of the tricuspid valves has certain special features. The right ventricle and auricle become functionally a common chamber. During ventricular systole the pressure rises to a high level; this is transmitted into the great veins near the heart with accompanying pulsatile swelling of the liver. It has recently been shown that the pressure beyond the last competent valves in the venous system may be considerably lower than the mean pressure in the central veins.^{2,55} This means, in effect, that blood is held up in the peripheral veins during ventricular systole and flows into the central venous pool in intermittent squirts during relaxation of the right ventricle. The last competent valves in the systemic veins proximal to the heart in fact replace the tricuspid valves.

Tricuspid incompetence may occur only in the last stages of heart failure but sometimes it may be present for years in patients who remain ambulant and who may be aware of relatively little breathlessness.

CARDIAC OEDEMA

The relationship of oedema to raised venous pressure remains a perennial problem. Undoubtedly hydrostatic factors are important in increasing the rate of filtration from the capillaries but it seems impossible to account for oedema on this factor alone. There is no relationship between the severity of oedema and the rise in venous pressure.¹ Gross rises of venous pressure have been produced in recent years by various operations designed to limit the spread of venous thrombosis and consequent embolism. Ray and Burch⁴⁴ have studied such cases following ligature of the iliac veins and the vena cava. Although the pressure in the veins of the legs was often enormously increased and sometimes

there was considerable accompanying oedema, it was observed that the venous pressure often remained considerably raised in the veins of the foot at a time when oedema was disappearing.

A recent attempt to explain some of the discrepancies has been made by Merrill.³⁸ It was found that the kidney blood flow was grossly reduced in heart failure; as a result of this there was a diminished volume of glomerular filtrate and a very considerable reabsorption of water and salt occurred in the normally functioning tubules. This led to a slowly accumulating salt retention and consequent increase in the water and salt content of the body with developing oedema.

Of the increased retention of salt in heart failure there can be no doubt, but whether it is entirely accounted for by primary reduction in renal blood flow and glomerular filtration rate, as suggested by Mokotoff and his colleagues,³⁹ is a matter of doubt. Similar reductions of cardiac output and renal blood flow are seen in patients with myxoedema⁸ in the absence of symptoms and signs of congestive failure. Similarly the hypothesis of diminished renal blood flow is somewhat strained when patients with so-called "high output heart failure" are considered. In severe anemia the renal plasma flow is normal although the blood flow may be slightly reduced. In other instances it is thought by Stead and his school⁶⁰ that the renal blood flow may become inadequate during daily work although it may be nearly normal at rest. These ingenious explanations may account for some of the discrepancies but a great deal more work is needed before we can reach a final assessment of the role of salt retention.

Other factors to be considered in cardiac oedema besides raised venous pressure and salt retention include:

Tissue Tension. When a normal individual stands upright, a certain amount of swelling of the lower limbs will occur, but this swelling does not exceed certain physiologic limits. These limits are imposed by tissue capacity and resistance to further

swelling. For cardiac oedema to develop something has to happen in the subcutaneous tissues to make them accommodate large quantities of fluid. What the process is is not yet clear. It may be partly accounted for by the tissue wasting which occurs in heart failure. Most oedematous patients show considerable loss of tissue, easily visible above the swollen parts of the body.

Diminution of Colloid Osmotic Pressure. The concentration of proteins in the plasma is often somewhat reduced and this no doubt contributes to the ease of filtration of fluid through the capillary walls.

Increased Extravascular Accumulation of Metabolites. In healthy man during exercise the increased formation of chemical products of low molecular weight in the active tissues tends to draw fluid from the blood stream. A similar process may play a part when the cardiac patient tries to take exercise, and furthermore a final equilibrium may not be so quickly established owing to the sluggish circulation.

Increased Permeability of Capillaries. This theory has often been invoked to explain cardiac oedema. Most of the old experiments on which this hypothesis was based involved the effect of total deprivation of oxygen on the capillary walls.²⁶ We now know that circulating blood in heart failure often returns to the right heart nearly half saturated with oxygen even in the late stages of heart failure. It would be difficult, therefore, to support the hypothesis that oxygen lack plays any important part in the production of increased capillary permeability. The protein content of oedema fluid does not suggest excessive permeability to protein.⁶⁵ Smirk⁵⁸ thinks that water and salts may pass through the capillary wall more easily and more quickly in congestive failure.

SOME OTHER CONSEQUENCES OF VENOUS CONGESTION

The liver often becomes swollen and the terminal picture of engorgement with disappearance of liver cells in the centres of

the lobules is well known. It is doubtful, however, if the degeneration of liver cells is, in fact, a consequence of pressure effects. It is more likely, as Bolton⁴ pointed out many years ago, to be the result of diminished blood flow through the liver. Jaundice is frequently present to a slight degree (serum bilirubin 1 to 2 mg. per 100 cc.) in the last stages. Sometimes it may become severe and the mechanism of this jaundice is still a matter of some perplexity. It has been thought that it results from the breakdown of red cells in infarcts in the lungs but there are many instances in which lung infarcts are present with no very significant degree of jaundice and conversely. Poor function of the liver may be suspected as a result of the diminished blood flow. A third factor which may be important is excessively high intravascular pressure within the liver itself which may interfere with the escape of bile from the channels between the liver cells.⁵⁷ It is highly probable that various factors are combined and that no single explanation is adequate. In advanced cases of long continued liver congestion a form of cardiac cirrhosis may develop. Often at this stage the jaundice is mild or slight but persistent ascites may become part of the picture. This is a well known phenomenon in constrictive pericarditis in which the occurrence of oedema and ascites is out of proportion to the dyspnoea.

The kidney in addition to circulatory disturbances already described becomes grossly congested. Leakage of albumin then occurs into the urine, often with the appearance of red cells as well.

CONCLUSION

A mechanism by which the venous pressure may be raised in heart failure is summarized in the diagram, and the evidence supporting this conception has been summarized. The writer realizes that there are still numerous perplexing difficulties surrounding the whole problem. He has thought it better, however, to define what seems to be a reasonable line of thought in keeping with the majority of established

facts rather than to overload the argument with conflicting and confusing ideas. In some cases the interpretations may be purely personal but in most instances the observations on which they are based have been substantiated by clinical experience and experiment. The writer expresses the deepest gratitude to all his collaborators and to many fellow workers in the same field in different parts of the world who, by continuous generous interchange of ideas, have helped to mould these opinions.

REFERENCES

1. ALTSHULE, M. D. The pathological physiology of chronic cardiac decompensation. *Medicine*, 17: 75, 1938.
2. BLOOMFIELD, R. A., LAUSON, H. D., COUNNAND, A., BREED, E. S. and RICHARDS, D. W. Recording of right heart pressure in normal subjects and in patients with chronic pulmonary disease and various types of cardiocirculatory disease. *J. Clin. Investigation*, 25: 239, 1946.
3. BLOOMFIELD, R. A., RAPOPORT, B., MILNOR, J. P. P. LONG, WALTER, K., MEBANE, J. GILMER and ELLIS, LAURENCE B. The effect of the cardiac glycosides upon the dynamics of the circulation in congestive heart failure. I. Ouabain. *J. Clin. Investigation*, 27: 388, 1948.
4. BOLTON, C. and BARNARD, W. G. Pathological occurrences in liver in experimental venous stagnation. *J. Path. Bact.*, 34: 701, 1931.
5. BRANDT, F. Die Abhängigkeit des Venendruckes von der Grösse der zirkulierenden Blutmenge, zugleich ein Beitrag zur Frage seiner klinischen Bedeutung. *Ztschr. f. klin. Med.*, 116: 398, 1931.
6. CHARLIER, R. and PHILIPOTT, E. Debit cardiaque et pression intraauriculaire pendant l'occlusion des carotides. *Compt. rend. Soc. de biol.*, 141: 201, 1947.
7. CHRISTIE, R. V. Dyspnoea: a review. *Quart. J. Med.*, 7: 421, 1938.
8. CORCORAN, A. C. and PAGE, I. H. Specific renal functions in hyperthyroidism and myxoedema. *J. Clin. Endocrinol.*, 7: 801, 1947.
9. COUNNAND, A. Personal communication.
10. DOCK, W. and TAINTER, M. L. Circulatory changes after full therapeutic doses of digitalis, with critical discussion of views on cardiac output. *J. Clin. Investigation*, 8: 467, 1930.
11. DONEGAN, J. F. The physiology of the veins. *J. Physiol.*, 55: 226, 1921.
12. DOUPE, J., KRYNAUW, R. A. and SNODGRASS, S. R. Some factors influencing venous pressure in man. *J. Physiol.*, 92: 383, 1938.
13. DRURY, A. N. and JONES. Rate at which oedema forms when veins of human limb are congested. *Heart*, 14: 55, 1927.
14. FLEISCH, A. Venomotorenzentrum und Venenreflexe. I Mitteilung. *Pflüger's Arch.*, 225: 26, 1930.
15. FLEISCH, A. Venomotorenzentrum und Venenreflexe. II Mitteilung. Blutdruckzügler und Venenreflexe. *Pflüger's Arch.*, 226: 393, 1931.
16. GIBSON, J. G. and EVANS, W. A., JR. Clinical studies of blood volume. III. Changes in blood volume venous pressure and blood velocity rates in chronic congestive heart failure. *J. Clin. Investigation*, 16: 851, 1937.
17. GOLLWITZER-MEIER, K. and BOHN, H. Über die venoconstrictorische Wirkung der Kohlensäure und ihre Bedeutung für den Kreislauf. *Klin. Wchnschr.*, 9: 872, 1930.
18. GOLTZ, F. Ueber den Tonus der Gefässe und seine Bedeutung für die Blutbewegung. *Virchows Arch.*, 29: 394, 1864.
19. HAMILTON, W. F., WOODBURY, R. A. and VOGT, E. Differential pressures in the lesser circulation of the unanaesthetised dog. *Am. J. Physiol.*, 125: 130, 1939.
20. HICKAM, J. B. and CARGILL, W. H. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J. Clin. Investigation*, 27: 10, 1948.
21. HOWARTH, S., McMICHAEL, J. and SHARPEY-SCHAFER, E. P. The circulatory action of theophylline ethylene diamine. *Clin. Sc.*, 6: 125, 1947.
22. HOWARTH, S., McMICHAEL, J. and SHARPEY-SCHAFER, E. P. Effects of oxygen venesection and digitalis in chronic heart failure from disease of the lungs. *Clin. Sc.*, 6: 187, 1947.
23. HOWARTH, S., McMICHAEL, J. and SHARPEY-SCHAFER, E. P. Effects of venesection in low output heart failure. *Clin. Sc.*, 6: 41, 1946.
24. KATZ, L. N., ROBBARD, S., FRIEND, M. and ROTTSMAN, W. Effect of digitalis on anaesthetised dog: action on splanchnic bed. *J. Pharmacol. & Exper. Therap.*, 62: 1, 1938.
25. KRAYER, O. Versuche an insuffizienten Herzen. *Arch. f. exper. Path. u. Pharmacol.*, 162: 1, 1931.
26. LANDIS, E. M. Micro injection studies of capillary permeability. III. The effect of lack of oxygen and the permeability of the capillary walls to fluid and to the plasma protein. *Am. J. Physiol.*, 83: 528, 1928.
27. LANDIS, E. M. BROWN, E., FAUTEUX, M. and WISE, C. Central venous pressure in relation to cardiac "competence," blood volume and exercise. *J. Clin. Investigation*, 25: 237, 1946.
28. LAUSON, H. D., BLOOMFIELD, R. A. and COUNNAND, A. The influence of respiration on the circulation in man with special reference to pressures in the right auricle, right ventricle, femoral artery and peripheral veins. *Am. J. Med.*, 1: 315, 1946.
29. LEWIS, T. and LANDIS, E. M. Some physiological effects of sympathetic ganglionectomy in human being and its effect in cases of Raynaud's malady. *Heart*, 15: 151, 1930.
30. LILJESTRAND, G., LYSHOLM, E. and NYLIN, G. The immediate effect of muscular work on the stroke and heart volume in man. *Skandinav. Arch. f. Physiol.*, 80: 265 1938.
31. LILJESTRAND, G. and LYSHOLM, E. (et al). The normal heart volume in man. *Am. Heart J.*, 17: 406, 1939.
32. LYSHOLM, E., NYLIN, G. and QUARNO, K. The relation between the heart volume and stroke volume

- under physiological and pathological conditions. *Acta radiol.*, 15: 237, 1934.
33. McMICHAE, J. The output of the heart in congestive failure. *Quart. J. Med.*, 7: 331, 1938.
 34. McMICHAE, J. Pharmacology of the failing human heart. *Brit. M. J.*, 2: 927, 1948.
 35. McMICHAE, J. Circulatory failure. *Schweiz. med. Wchnschr.*, 76: 851, 1946.
 36. McMICHAE, J. and SHARPEY-SCHAFER, E. P. The action of intravenous digoxin in man. *Quart. J. Med.*, 13: 123, 1944.
 37. McMICHAE, J. and SHARPEY-SCHAFER, E. P. Cardiac output in man by a direct Fick method. *Brit. Heart J.*, 6: 33, 1944.
 38. MERRILL, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of forward failure as the primary cause of edema. *J. Clin. Investigation*, 25: 389, 1946.
 39. MOKOTOFF, R., ROSS, G. and LEITER, L. Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. *J. Clin. Investigation*, 27: 1, 1948.
 40. PATTERSON, S. W., PIPER, H. and STARLING, E. H. The regulation of the heart beat. *J. Physiol.*, 48: 465, 1914.
 41. PETERS, J. P. Role of sodium in the production of edema. *New England J. Med.*, 353: 239, 1948.
 42. PRINZMETAL, M. Personal communication.
 43. PUGH, L. G. C. and SYNDHAM, C. The circulatory effects of mercurial diuretics in congestive heart failure. *Clin. Sc.*, 8: 1949 (in press).
 44. RAY, C. T. and BURCH, G. E. Vascular responses in man to ligation of the inferior vena cava. *Arch. Int. Med.*, 80: 587, 1947.
 45. RICHARDS, D. W., JR. Circulation in traumatic shock in man. *Bull. New York Acad. Med.*, 20: 363, 1944.
 46. RICHARDS, D. W., JR. Contributions of right heart catheterization in the physiology of congestive heart failure. *Am. J. Med.*, 3: 434, 1947.
 47. RICHARDS, D. W. JR., CAUGHEY, J. L., COUNNAND, A. and CHAMBERLAIN, F. L. Intravenous saline infusion as a clinical test for right heart and left heart failure. *Tr. A. Am. Physicians*, 52: 250, 1937.
 48. RICHARDS, D. W., JR., COUNNAND, A., DARLING, R. C., GILLESPIE, W. H. and BALDWIN, E. DE F. Pressure of blood in the right auricle in animals and in man under normal conditions and in right heart failure. *Am. J. Physiol.*, 136: 115, 1942.
 49. RIML, O. Über das Verhalten des Blutdruckes in der Vena Cava bei plötzlichem Zirkulationstillstande. *Arch. f. exper. Path. u. Pharmacol.*, 139: 231, 1929.
 50. ROOS, A. and SMITH, J. R. Production of experimental heart failure in dogs with intact circulation. *Am. J. Physiol.*, 153: 558, 1948.
 51. ROY, C. S. and SHERRINGTON, C. S. On the regulation of the blood supply of the brain. *J. Physiol.*, 2: 85, 1890.
 52. RYTAND, D. A. Effect of digitalis on venous pressure of normal individuals. *J. Clin. Investigation*, 12: 847, 1933.
 53. SCHOTT, E. Die Erhöhung des Druckes im venösen System bei Anstrengung als Mass für die Funktionstüchtigkeit des menschlichen Herzens. *Deutsche Arch. klin. Med.*, 108: 537, 1912.
 54. SHARPEY-SCHAFER, E. P. Cardiac output in severe anaemia. *Clin. Sc.*, 5: 125, 1944.
 55. SHARPEY-SCHAFER, E. P. Unpublished data on tricuspid incompetence.
 56. SHARPEY-SCHAFER, E. P. Transfusion and the anaemic heart. *Lancet*, 2: 296, 1945.
 57. SHERLOCK, S. P. V. Jaundice in heart failure. *Quart. J. Med.*, 14: 222, 1945.
 58. SMIRK, F. H. Observations on the causes of oedema in congestive heart failure. *Clin. Sc.*, 2: 317, 1935.
 59. STARR, I., JEFFERS, W. A. and MEADE, R. H. The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog with a discussion of the relation between clinical congestive heart failure and heart disease. *Am. Heart J.*, 26: 291, 1943.
 60. STEAD, E. A., JR., WARREN, J. V. and BRANNON, E. S. Effect of lanatoside C on the circulation of patients with congestive failure. A study using catheterization of the right side of the heart. *Arch. Int. Med.*, 81: 282, 1948.
 61. STEAD, E. A., JR., WARREN, J. V. and BRANNON, E. S. Cardiac output in congestive heart failure. An analysis of the reasons for lack of correlation between the symptoms of heart failure and the resting cardiac output. *Am. Heart J.*, 35: 529, 1948.
 62. STEAD, E. A. (et al). Unpublished observations.⁵⁹
 63. SZEKELY, P. Venous pressure responses to exercise. *Am. Heart J.*, 22: 360, 1941.
 64. WARREN, J. V., BRANNON, E. S., STEAD, E. A., JR. and MERRILL, A. J. Effect of venesection and pooling of blood in extremities on atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in 3 instances. *J. Clin. Investigation*, 24: 337, 1945.
 65. WARREN, J. V. and STEAD, E. A., JR. Protein content of edema fluid in patients with acute glomerulonephritis. *Am. J. M. Sc.*, 208: 618, 1944.
 66. WARREN, J. V., BRANNON, E. S., STEAD, E. A., JR. and MERRILL, A. J. Pericardial tamponade from stab wound of the heart and pericardial effusion or empyema. A study using the method of right heart catheterization. *Am. Heart J.*, 31: 418, 1946.
 67. WIGGERS, C. J. Pressure Pulses in the Cardiovascular System. London, 1928. Longmans, Green & Co.
 68. WOOD, P. and PAULETT, J. The effect of digitalis on the venous pressure. *Brit. Heart J.*, 11: 83, 1949.
 69. WOOD, W. B. and JANEWAY, C. A. Change in plasma volume during recovery from congestive heart failure. *Arch. Int. Med.*, 62: 151, 1938.
 70. YOKOTA, M. Über die Wirkung der Arzneimittel auf den Blutdruck besonders den Venösen. *Tohoku J. Exper. Med.*, 4: 23, 1923.

Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE MIDWESTERN SECTIONAL MEETING

HELD IN CHICAGO, THURSDAY, OCTOBER 28, 1948

GASTRIC SECRETORY RESPONSE TO INTRAVENOUSLY ADMINISTERED AMINO ACID MIXTURES. *Paul R. Sharick, M.D. (by invitation) and Darrell A. Campbell, M.D., Eloise, Michigan.*

Individual amino acids given intravenously produce hypoglycemia and a marked acid response due to a mechanism involving the vagus nerves. The humoral-neural mechanism of gastric stimulation due to intravenous amino acids was confirmed in dogs whose non-vagal pouches were proven by use of the insulin test.

Twelve patients were given rapid intravenous infusions of amino acid mixtures, six receiving a commercial enzymatic protein hydrolysate and six a commercial solution of the ten essential amino acids with added glycine. Eight patients had an active peptic ulcer and four patients were without gastric disease. In all patients administration of amino acid mixtures increased free and total gastric acidity. The acid response was variable and approached that following insulin hypoglycemia in only a few cases. In one case the response was abolished by subsequent vagotomy for peptic ulcer. Regurgitation of bile occurred in all cases.

No significant difference was found with the two amino acid preparations used. No correlation was found between blood amino acid nitrogen levels and gastric acid stimulation. In seven instances a moderate volume secretory response was obtained. An initial transitory increase in blood sugar occurred.

Amino acid mixtures are currently being used in the treatment of peptic ulcer. It is suggested that this plan of therapy may be contraindicated due to the gastric acid response. The hypermotility and acid stimulation produced by intravenously administered amino acids calls for caution in their use following gastrointestinal surgery. The concurrent administration of oral antacids may be advisable in such patients.

USE OF THE ALBUMIN FRACTION IN THE ECLAMPTOGENIC TOXEMIAS. *Allen C. Barnes M.D. and (by invitation) Fred B. Hapke, M.D., Columbus, O. (From the Department of Gynecology-Obstetrics, Ohio State University Medical School.)*

In normal pregnancy there is a drop in the serum albumin level with a shift of the A/G ratio; in the pre-eclamptic and eclamptic toxemias of pregnancy these changes in albumin are accentuated, with the A/G ratio approaching 1.

The clinical response to albumin replacement has been reported in the toxemias of pregnancy. The present study is concerned entirely with the fate of such injected albumin in the eclamptogenic toxemias and the effect this treatment has on the patient's protein status. Thirty patients were placed on a diet low in salt and high in protein and were given oral ammonium chloride and high fluid intake. After the patient's condition had stabilized on this regimen (at least three days) the albumin fraction was administered. Changes in total proteins, A/G ratio, plasma volume, electrophoretic picture, hematocrit, urinary volume and albuminuria, as well as changes in blood pressure, weight and symptomatology were noted.

Results to date indicate that the injection of albumin fraction causes a temporary rise in total serum protein levels. During the next forty-eight hours the blood levels drop and there is an increase of albumin loss in the urine, indicating that much of the injected albumin is lost through the kidneys. This increase in albumin excretion is accompanied by a moderate diuresis, and the clinical observations seemed to accompany this temporary increase in urinary output. The alterations in the patient's serum proteins were all temporary; there was no change in blood pressure and no significant evidence of clinical improvement.

This study indicates that elevation of the serum albumin level in patients with the ec-

lamptogenic toxemias is not a specific in the management of the condition.

MERCURY EXCRETION FOLLOWING ORAL MERCURIAL DIURETICS IN MAN. *E. R. Huffman, M.D. (introduced by Charley J. Smyth, M.D.), Eloise, Michigan.*

Information concerning the route and rate of elimination of mercury following the ingestion of oral mercurial diuretics is limited. Eighteen hospitalized cardiac patients in congestive failure received oral mercurhydrin for four or more consecutive four-day periods, and the excretion of mercury in the stools and urine was determined for periods up to sixteen days following the last dose. The oral diuretic was administered in two forms, a slowly dissolving enteric coating, and in combination with cevita-mic acid and coated with a rapidly dissolving sugar coating. The mercury content of the urine and feces was determined by the dithizone method.

When one tablet per day of the slowly dissolving drug containing 39 mg. per tablet was given, the urinary excretion of mercury for the four days of treatment ranged from 2.52 mg. (1.5 per cent) to 4.99 mg. (3.2 per cent); the elimination of mercury in the feces ranged from 98.96 mg. (63.0 per cent) to 152.50 mg. (97.8 per cent). When five tablets were given per day, the urinary excretion of mercury ranged from 1.98 mg. (0.27 per cent) to 20.35 mg. (2.7 per cent) and the fecal mercury ranged from 190.44 mg. (24.5 per cent) to 640.0 mg. (82.0 per cent). When the larger doses of mercury were given, the average daily excretion of mercury in the urine was only 2.41 mg. When five tablets per day of the rapidly dissolving mercury complex containing 19.5 mg. of mercury per tablet were given, the urinary excretion of mercury during the four days of treatment ranged from 0.8 mg. (0.2 per cent) to 8.8 mg. (2.3 per cent). The elimination of mercury in the feces during this same interval ranged from 90.7 mg. (23.3 per cent) to 240.0 mg. (61.5 per cent).

Follow-up studies of mercury excretion indicate a significant delayed excretion of mercury lasting up to sixteen days following the last dose. These data show that with oral administration of mercurial diuretics there is an accumulation of mercury in the body which is slowly excreted. Only minimal quantities of mercury appear in the urine.

MAY, 1949

RENAL HEMODYNAMICS IN HEART DISEASE. *B. I. Heller, M.D. and (by invitation) W. E. Jacobson, M.D., Minneapolis, Minnesota.* (From the Department of Medicine, Veterans Hospital and the University of Minnesota Hospitals.)

Renal hemodynamic studies were performed by use of the para-amino hippurate and mannitol clearance methods in thirty-eight male patients with organic heart disease. Patients with hypertension were excluded. The patients were divided into the following three groups: group A, thirteen patients with rheumatic valvular heart disease without previous or present evidence of heart failure; group B, twelve patients admitted with cardiac decompensation but clinically compensated at the time of study; group C, thirteen patients with cardiac decompensation.

In all phases of heart disease there was a disproportionate reduction in the effective renal plasma flow and glomerular filtration rate. This change was most marked in patients with congestive heart failure, and the resultant increase in the filtration fraction indicates a high degree of efferent arteriolar spasm. The cause of this vasospasm is unknown.

It has been generally conceded that tubular function is normal in congestive heart failure. Therefore, the reduction of maximal tubular excretory capacity in group C patients was of great interest. It appears most likely that tubular ischemia accounts for this reduction.

EFFECTS OF MORPHINE ON RENAL CLEARANCES OF PARA-AMINO HIPPURATE AND SODIUM THIOSULFATE IN THE HUMAN KIDNEY. *Willis E. Brown, M.D., Robert Hodges, M.D. and J. T. Bradbury, Sc.D., Iowa City, Iowa.* (From the Department of Obstetrics and Gynecology, University of Iowa College of Medicine.)

Morphine antidiuresis has been previously reported by us. The mechanism of this reduction seems to be independent of sedation, hypnosis, induced sleep or postpituitary hormone release.

Using the renal clearances of para-amino hippurate and thiosulfate as a measure of renal plasma flow and glomerular filtration, respectively, we have found that morphine given intravenously in doses of 16 mg. produced the

following effects: (1) a consistent and significant lowering of urine flow; (2) a reduction in the renal plasma flow; (3) no significant change in glomerular filtration; (4) a slight rise in filtration fraction; (5) an increased re-absorption fraction resulting in decreased urine output.

We believe that the antidiuretic effect of morphine is largely due to this increase in the re-absorption fraction.

These observations showing decreased clearance of para-amino hippurate (a cortical function) and increased tubular re-absorption of water (a medullary function) are compatible with the vascular shunt theory of Truett.

ADMINISTRATION OF TETRAETHYLAMMONIUM BROMIDE BY SLOW CONTINUOUS INTRAVENOUS INFUSION. *C. W. Ulrich (by invitation), J. D. Peirce, Jr., M.D. and K. G. Kohlstaedt, M.D., Indianapolis, Indiana.*

Since the effect of a single intravenous injection of TEAB is brief and is often accompanied by a marked decline in blood pressure, the safety and practicability of a continuous intravenous infusion of the drug was investigated. With TEAB entering the vein at the rate of 6 to 10 mg. per minute, a definite rise in skin temperature could be maintained for six to eight hours in normotensive and in hypertensive persons. Arterial pressure was reduced very little or not at all. Side effects did not occur until the infusion rate exceeded 7 mg. per minute and when more than 12 mg. per minute were given; all subjects exhibited mild untoward symptoms. The maximum amount of TEAB administered was 16 mg. per minute. In normotensive persons at this rate of infusion a mean rise of 5°C. was produced in the skin temperature over the great toe. In patients with thrombo-angiitis obliterans or with obliterative arteriosclerosis the continuous infusion of 6 to 13 mg. of TEAB per minute gave moderate to complete relief from pain and the mean rise in skin temperature was never more than 3°C. This method of administration was also used to control intractable diarrhea in two persons with ulcerative colitis. If the rate of infusion is accurately controlled by a Harvard tunnel clamp, intravenous administration of TEAB can be maintained for at least eight hours, with few if any unpleasant reactions.

MINIMAL SODIUM DIET; A CONTROLLED STUDY OF ITS EFFECT UPON THE BLOOD

PRESSURE OF AMBULATORY HYPERTENSIVE SUBJECTS. *Milton Landowne, M.D. (by invitation) Walter Thompson, Jr., M.D. and (by invitation) Barbara Ruby, B.S., Chicago, Illinois.*

Administration of a diet rigidly restricted in sodium may influence the habits and reactions of the patient profoundly, altering blood pressure through mechanisms unrelated to the sodium restriction *per se*. A controlled evaluation of these factors in the non-hospitalized patient is needed. Accordingly, twenty-one hypertensive subjects were placed on an adequate diet containing less than 300 mg. of sodium per day and were followed for approximately eighteen weeks. Weekly blood pressure and twenty-four-hour urine analyses were made. All subjects received medication consisting either of 4 Gm. of NaCl a day or placebos. At six-week intervals the medication was either changed or continued according to pre-arranged schedules established by the pharmacist.

The experiment thus consisted of three periods, differing only in that during one (or two) period(s) supplemental sodium chloride was administered, while in two (or one) period(s) the sodium intake remained at a bare minimum. Neither the investigator nor the subject was aware of the nature of the medication.

Satisfactory data were available from only eight of the subjects. The criteria for their selection required that the twenty-four-hour urinary sodium average below 500 mg. for at least one period and over 1,000 mg. for at least one period. The average systolic and diastolic blood pressure during rigid sodium restriction was 4.96 and 4.72 mm. of Hg lower than during the periods of added sodium, respectively. These data appear to be significant statistically.

In summary, a diet rigidly restricted in sodium is difficult to administer successfully to ambulatory hypertensive subjects. A difference of less than 5 mm. Hg in average blood pressure was observed, ascribable to the effect of NaCl restriction alone.

PROGNOSIS IN UNTREATED ARTERIAL HYPERTENSION: REPORT ON ONE HUNDRED SEVENTEEN PATIENTS UNDER FIFTY-THREE YEARS OF AGE FOLLOWED FOR EIGHT TO TEN YEARS. *Arthur H. Griep, M.D., (by invitation) George R. Barry, M.D. and*

(by invitation) *Winston C. Hall, M.D., Ann Arbor, Michigan.* (From the Department of Internal Medicine, University of Michigan Medical School.)

One hundred seventeen patients (forty-four males and seventy-three females) with essential hypertension were followed for eight to ten years. All had been carefully studied initially and were suitable candidates for sympathectomy or medical treatment. Primary renal disease was excluded and the blood pressure was above 160 mm. systolic and 110 mm. diastolic. When possible, the living patients were re-examined and a history, physical examination, electrocardiogram, teleoroentgenogram, urinalysis, urine concentration test, urea clearance and ophthalmologic examination were carried out.

The average age at the start of the interval was 43.7 years for the males and 41.3 for the females. There was a gross mortality rate of 53.8 per cent and a corrected rate of 50.3 per cent. There was a 70 per cent mortality in males as compared with 43 per cent for the females.

Eighty-eight per cent of the patients showed less than 40 mm. systolic and 15 mm. diastolic change in blood pressure. In one case the blood pressure fell to normal levels without known cause. Patients with blood pressures above 200 mm. systolic and 130 mm. diastolic, with decreased functional capacity of the heart, cardiac enlargement, abnormal electrocardiogram, abnormal urinalysis and funduscopy abnormalities, sustained a higher mortality rate. In this group of patients the most common cause of death was cerebrovascular accident (39.6 per cent) and cardiac failure (28.5 per cent).

Of fifty-one patients living 19 per cent are symptom-free at the present time. Sixty-one per cent are mildly symptomatic but can carry on with their daily work. Seventeen per cent are ambulatory but unable to work. One patient is bedridden and the symptoms and working capacity of two patients are unknown.

OBSERVATIONS ON THE EFFECT OF A HIGH FLUID INTAKE IN VALVULAR HEART DISEASE IN THE LAST TRIMESTER OF PREGNANCY. *W. W. Hurst, M.D. (by invitation), F. L. McPhail, M.D. and F. R. Schemm, M.D., Great Falls, Montana.*

Observations were made during twenty-two periods in eighteen pregnancies of seventeen patients with severe rheumatic heart disease. All had classical signs of mitral stenosis, six with aortic insufficiency and two with subacute bacterial endocarditis. All exhibited signs of myocardial failure other than edema of the lower extremities before therapy was begun, while one had profuse pulmonary edema, one permanent auricular fibrillation and 6 transient fibrillation. Two of the eighteen pregnancies were terminated by cesarean sections; labor was spontaneous in seven and induced in nine.

The average length of the twenty-two periods was twelve days, the maximum thirty days; the average daily intake was 3,000 cc. or over in nineteen periods, more than 4,000 cc. daily in eight and from 5,000 to 6,000 cc. in four of the periods. In nine of the twenty-two periods intravenous fluids were given to supplement oral intake, in amounts of from 500 to 3,000 cc. in twenty-four hours. In two instances 16,000 and 14,500 cc. of fluid were given by vein in two eight-day periods. Isotonic dextrose in distilled water was used except when emesis or duodenal drainage called for sodium chloride replacement.

The combination of marked mitral stenosis and near-term pregnancy should put the heart at a maximum mechanical disadvantage. Yet there was no evidence that the rather large amounts of plain water given, in these twenty-two observations to maintain an adequate water balance, either hindered the clearing of heart failure or embarrassed the circulation.

UNIPOLAR ELECTROCARDIOGRAPHIC STUDY OF LEFT VENTRICULAR HYPERTROPHY. THE ELECTROCARDIOGRAM WITH LEFT AXIS DEVIATION. *Ernest Goulder, M.D. and (by invitation) Wright Adams, M.D., Chicago, Illinois.*

This study presents ninety-four selected cases in which the electrocardiogram was characterized by left axis deviation with an rS type of QRS in lead III and in which the six multiple precordial leads of Wilson (V leads) and the three augmented extremity leads of Goldberger (AV leads) were used to supplement the three standard leads.

A survey of the group as a whole permitted classification of all tracings into four major categories on the basis of two fundamental criteria in lead aVL: (1) An R wave 9 mm. or

more in amplitude and (2) a ratio, expressed in per cent, of the amplitude of T to the amplitude of R that was less than 10 per cent (T/R ratio).

The first group was characterized in lead aVL by an R wave less than 9 mm. and by a T/R ratio greater than 10 per cent and was also associated with normal standard and unipolar leads. Clinically, this group was not correlated with left ventricular hypertrophy. The second group was characterized in lead aVL by an R wave greater than 9 mm. in amplitude and by a negative T/R ratio due to an inverted T wave. Most of the patients in this group presented in the standard leads the left ventricular strain pattern of Barnes and Whitten. All showed an excellent correlation with disease processes known to be associated with this pattern. The third group was characterized in lead aVL by an R wave in excess of 9 mm. and by a T/R ratio less than 10 per cent due to a relatively low upright T wave. Many of these tracings were associated with a left ventricular hypertrophy pattern in the standard leads in which a low T-I was associated with an upright T-III, but in others the abnormality of the T waves in the standard leads was less readily expressed. This group showed a good correlation clinically with disease processes associated with left ventricular hypertrophy. The fourth group was characterized in lead aVL either by an R wave greater than 9 mm. or by a T/R ratio less than 10 per cent and clinically had a poorer correlation with left ventricular hypertrophy.

The utilization of these two criteria in lead aVL appears to be a useful adjunct in the electrocardiographic evaluation of left ventricular hypertrophy.

EFFECT OF POSITION ON THE Q-T COMPLEX IN THE WOLFF-PARKINSON-WHITE SYNDROME AND BUNDLE BRANCH BLOCK. *Saul L. Silver, M.D. (by invitation) Simon Zivin, M.D. (by invitation), and Theodore R. Van Dellen, M.D., Chicago, Illinois.*

Eighteen cases of Wolff-Parkinson-White syndrome were collected and the patients' electrocardiograms compared with the typical bundle branch block. Lead I was taken in all patients in the reclining left and right lateral positions. Similar changes occurred when the position was changed in those with Wolff-Parkinson-White syndrome and in the eight

patients with bundle branch block. These similarities suggest that the two conditions are related and lend evidence to the observation that Wolff-Parkinson-White syndrome is not entirely benign.

COMPLEMENT-FIXATION STUDIES WITH YEAST-PHASE ANTIGEN IN EXPERIMENTAL HISTOPLASMOSIS. *Chris J. D. Zarafonetis, M.D., Ann Arbor, Michigan.*

Diagnosis of histoplasmosis can be made with certainty only by the isolation and identification of the causative fungus, *Histoplasma capsulatum*. Since material suitable for culture is not always readily accessible, other diagnostic aids have been sought. A skin test for histoplasmosis was introduced in 1941 but has been found to have little or no clinical value. The purpose of this report is to present preliminary observations on another possible diagnostic aid, namely, the complement-fixation test.

The antigens employed in this study consisted of suspensions of yeast-phase organisms grown on sealed blood-agar slants or in liquid Dubos media containing albumin. The organisms were killed, harvested and repeatedly washed by centrifugation and resuspension in physiologic saline solution containing 0.1 per cent formalin.

Groups of rabbits and guinea pigs were inoculated with suspensions of living yeast-phase organisms. Antisera were obtained by periodic bleeding of the animals and selected sera were used for the titration of antigens. The test used employs serial two-fold serum dilutions, two antigen units and two full units of complement. After overnight refrigeration the hemolytic system is added. This consists of equal parts of a 3 per cent suspension of sheep erythrocytes and amboceptor diluted to contain three hemolytic units. After one-half hour at 37°C. the test is read in the customary manner.

Tests were performed on sera from the inoculated animals and a progressive rise in antibody titer was detected in every instance. Assuming that the antigen is specific, this is considered a diagnostic response. Sera from humans hospitalized for various disorders were also tested. A surprising number of such sera fixed complement in low dilution. Before the test may be utilized for clinical or epidemiologic studies, however, its specificity must be demonstrated through additional studies.

EXPERIENCE WITH DARVISUL (PHENOSULFAZOLE) IN THE TREATMENT OF CLINICAL AND EXPERIMENTAL POLIOMYELITIS. *Morris Schaeffer, M.D.* and (by invitation) *John A. Toomey, M.D., Cleveland, Ohio.* (From the Department of Pediatrics, Western Reserve University and Contagious Department of City Hospital.)

A new sulfonamide compound, phenosulfazole, said to be therapeutically beneficial in poliomyelitis was administered parenterally and orally to sixty-eight patients at the onset of the acute phase of poliomyelitis. The outcome in these patients was compared with sixty-nine untreated control patients selected alternately on admission. No evidence was obtained that the natural course of the disease was affected by this treatment.

Similarly, in the experimental disease produced in 150 mice with the Lansing strain of poliomyelitis virus, administration of phenosulfazole prior to or simultaneously with infection failed to prevent paralysis or death in the treated animals.

PRELIMINARY REPORT ON THE PULMONARY CIRCULATION IN BRONCHIAL ASTHMA. *H. A. Zimmermann, M.D., Cleveland, Ohio.*

A series of five patients with typical attacks of bronchial asthma was studied by means of intracardiac catheterization of the pulmonary artery by the method of Courmand. Pulmonary arterial pressures, femoral or brachial arterial pressures, the electrocardiogram and phase of respiration with a superimposed time trace were recorded simultaneously. This was done by means of pressure transmitters, strain gages, strain amplifiers and a six-channel, direct-writing Brush oscillograph. Cardiac outputs were determined by the Fick principle using the Scholander method for blood oxygen levels and the Rahn method using a Pauling oxygen analyzer for determination of the amount of oxygen in the expired air.

All patients had a moderate to severe attack of bronchial asthma and all had abnormally high pressures in the pulmonary artery. One patient had a few wheezes in the chest with normal pulmonary arterial pressure, but after an injection of mecholyl a moderately severe attack of asthma was induced and the pulmonary arterial pressure was elevated above normal.

Aminophylline may relieve an acute attack of bronchial asthma and the pulmonary arterial pressure drops to a subnormal level. Adrenalin, on the other hand, may relieve an acute attack of bronchial asthma but it causes a distinct elevation in the pulmonary arterial pressure. In patients whose asthmatic attacks were relieved we have found that the cardiac output was higher following the use of adrenalin than following aminophylline.

FIBRINOLYSIS AND PROTHROMBIN IN EXPERIMENTAL APPENDICEAL PERITONITIS. *Carlos Tanturi, M.D., Raymond Anderson, M.D.* and *Nicholas Wetzel, M.D., (introduced by Walter J. Maddock, M.D.), Chicago, Illinois.* (From the Department of Surgery, Northwestern University Medical School.)

Appendiceal peritonitis was produced in forty-six dogs using the technic of Bowes. Serum fibrinolytic activity was studied pre- and post-operatively using the method of Kay and Lockwood. Variations in blood prothrombin were measured by the technic of Tanturi and Banfi.

Results showed that a decrease in prothrombin is observed in appendiceal peritonitis in 85.7 per cent of the dogs, indicating some degree of injury to the liver. Forty-six per cent of the dogs showed fibrinolytic activity in the serum during the postoperative period. A decrease in prothrombin bears a closer relationship to death than does any variation in the fibrinolytic-antifibrinolytic equilibrium. An early postoperative decrease in prothrombin corresponded with a higher incidence of death. Chloroform anesthesia was given in ten dogs to increase liver damage. These dogs died earlier than those dogs who received no chloroform although no increase in fibrinolysis or hypoprothrombinemia was observed.

The decrease in prothrombin is not the cause of death but appears to be the reflection of the primary cause of death in the animal more than the fibrinolytic activity of the blood.

ESTIMATION OF MEGAKARYOCYTE CONTENT OF ASPIRATED STERNAL MARROW. *Lawrence Berman, M.D. (by invitation), Arnold R. Axelrod, M.D. (by invitation) Else S. Kumke, B.S., Detroit, Michigan.* (From the Departments of Pathology and Medicine,

Wayne University College of Medicine, and the City of Detroit Receiving Hospital.)

The present methods of estimating the megakaryocyte content of aspirated sternal bone marrow are not satisfactory. Methods based on examination of marrow smears are unsatisfactory because the aspirated marrow is unavoidably diluted with sinusoidal blood; the distribution of megakaryocytes on smears is irregular; the total nucleated cell content of bone marrow is variable from patient to patient and the incidence of megakaryocytes may vary independently of the incidence of other nucleated cells. Hemocytometer counts of megakaryocytes are subject to error introduced by variable dilution with sinusoidal blood and also by the variable base of total nucleated cells.

The present study showed that neither the smear nor chamber count method yields results which correlate with those obtained by study of actual marrow tissue sections. Instances of low counts obtained by the smear or chamber methods in patients with high megakaryocyte content, as revealed in marrow sections, were encountered. Even the section count produces arbitrary values which cannot be converted into terms expressive of the actual number of megakaryocytes per unit volume of marrow. Hence all section counts obtained from patients must be compared with counts made by identical means from suitable controls.

Since the error of underestimating the megakaryocyte content of aspirated marrow samples may be of clinical importance, especially when the question of splenectomy for thrombocytopenic purpura is presented, examination of marrow sections for megakaryocytes should not be omitted whenever the chamber or smear methods yield values suggestive of decreased megakaryocytopoiesis.

CLINICAL EVALUATION OF TETRAETHYLAMMONIUM CHLORIDE IN CORONARY HEART DISEASE. *Harold W. Christy, M.D., (introduced by Howard A. Lindberg, M.D.), Chicago, Illinois.*

Ten patients presenting symptoms that were considered classical of chronic coronary insufficiency with the anginal syndrome, most of whom had abnormal electrocardiograms, were treated with bi-weekly intramuscular injections

of tetraethylammonium chloride. The dosage ranged from 200 to 800 mg. per injection. No reactions of moment were encountered in this group. Some of the patients received injections over a period of at least a year. Two patients had complete disappearance of their anginal syndrome with improvement in the electrocardiogram during the course of treatment. Five patients reported considerable improvement in their symptoms. None developed what might be considered anginal equivalents. Two had improvement in their electrocardiograms. Two patients reported no improvement whatsoever and one of them was the only one that did not have electrocardiographic or physical findings to support a diagnosis of coronary insufficiency. The tenth patient did not report for continuation of therapy and the results of treatment in this case are not known.

CAUSES OF DEATH IN ANEURYSMS OF THE HEART. *Wendell A. Shullenberger, M.D., Indianapolis, Indiana.* (From the Division of Internal Medicine, Methodist Hospital.)

It is frequently stated that cardiac aneurysm is not incompatible with a considerable degree of physical activity and it is a fact that despite their spectacular pathologic features these aneurysms when fully healed and fibrosed undergo rupture infrequently. The usual causes of death following establishment of this condition in the heart are congestive failure, rupture and "sudden death." The last group deserves more attention than it has received. The case reported here is believed to be unusual in the nature of the terminal event.

A diagnosis of acute coronary thrombosis was made in a fifty year old male after he had suffered three attacks of epigastric pain in a period of eleven days. Aneurysm of the left ventricle was diagnosed by roentgenogram after three weeks in the hospital. He became ambulatory and carried on fairly normal business activities for thirteen months but died suddenly after several attacks of epigastric pain. Autopsy showed a large aneurysm of the left ventricle and a fresh thrombosis of the circumflex branch of the right coronary artery.

Statistics obtained from analysis of forty-six well studied cases selected from the literature show that somewhat less than 50 per cent of patients may be expected to survive from a few months to several years. It is further shown that

when aneurysm of the heart has been established, 46 per cent died of congestive failure, 11.5 per cent of rupture of the aneurysm, 11.5 per cent of acute coronary thrombosis, 8 per cent of left ventricular failure and 8 per cent of other causes. The remaining 15 per cent are classified as "sudden deaths."

AN ENDOCRINE FINDING APPARENTLY CHARACTERISTIC OF GOUT. VERY LOW URINARY 17-KETOSTEROID EXCRETION, WITH CLINICALLY NORMAL ANDROGENIC FUNCTION. *W. Q. Wolfson, M.D., R. Levine, M.D., H. S. Guterman, M.D., C. Cohn, M.D., H. D. Hunt, M.D. and E. F. Rosenberg, M.D., Chicago, Illinois.* (From the Department of Biochemistry and the Department of Metabolic and Endocrine Research, Medical Research Institute, Michael Reese Hospital; the Arthritis Clinic and the Division of Medicine, Michael Reese Hospital, Chicago; and the Department of Internal Medicine, Albany Medical College, Albany, N. Y.)

The urinary 17-ketosteroids (KS) are the chief identified urinary excretory products of male sex hormone metabolism. Urinary KS values depend upon both testicular and adrenal androgen production in men and upon adrenal androgen production in women.

Decreased urinary KS output has been found in all of a group of eleven gout patients (average 3.0 mg./day). Decreased excretion occurred in all phases of the disease including asymptomatic gout. Similar decreases did not occur in patients with idiopathic hyperuricemia and in males with rheumatoid polyarthritis or spondylitis.

Review of currently available endocrine explanations for decreased 17-ketosteroid output of the degree noted indicated none to be acceptable. Injected testosterone was recovered as urinary 17-ketosteroid to the usual extent and no defects in hepatic function were noted. Renal function was well enough preserved to make "retention" of 17-ketosteroids improbable. In spite of accumulating evidence that altered adrenocortical glycocorticoid production may be important in acute gouty attacks there was no evidence of "resistance stage" endocrine status at other periods.

Biologic evidence of androgen activity was normal in nine of the ten men in this group. A

review of a much larger series of patients gave additional evidence that hypogonadism is not clinically prominent in patients with gout.

The findings of very low outputs of urinary 17-ketosteroids in the presence of normal biologic androgen activity appears to be a new endocrine finding which is characteristic for gout. Our working hypothesis is that in gout biologic androgen activity is maintained by an androgenic hormone which does not make an important contribution to urinary 17-ketosteroids when metabolized.

COMPARATIVE SYMPATHETIC BLOCKING AND ADRENOLYTIC ACTION OF FOUR DRUGS IN THE HUMAN SUBJECT. *J. W. Avera, M.D. (by invitation), S. W. Hoobler, M.D., (by invitation) S. G. McClellan, M.D. and (by invitation), W. J. Little, M.D., Ann Arbor, Michigan.* (From the Department of Internal Medicine, University Hospital.)

Comparative effects of the intravenous injection of tetraethylammonium chloride (TEA), (6 mg./Kg. body weight); priscol, (0.6 mg./Kg. body weight); dihydroergocornine (DHO), (0.005–0.01 mg./Kg. body weight) and piperidomethyl benzodioxane (933F) (10 mg./square meter body surface) on peripheral blood flow were studied by means of venous occlusion plethysmograph. As a result of these studies we have arrived at the following conclusions:

Tetraethylammonium increases peripheral blood flow solely by a sympathetic blocking action. It does not produce vasodilatation in the denervated extremity and it has no adrenolytic effects. When injected intra-arterially, it has a slight vasoconstrictor action in concentrations well above those usually attained by intravenous injection.

Priscol increases blood flow by a direct vasodilator action. It has weak adrenolytic properties when given intravenously and a more marked effect when given intra-arterially. It probably has relatively little sympatholytic action when administered intravenously since the increase in blood flow in the innervated extremity is considerably less than that following paravertebral block or ganglionic blockade with tetraethylammonium and since the innervated and denervated extremity show approximately equal vasodilation following injection of the drug.

The increase in peripheral blood flow after

dihydroergocornine is, for similar reasons, probably not dependent on its sympathetic blocking properties. Since the vasodilator effect after intravenous injection was delayed in onset and since no increase in blood flow occurred on intra-arterial injection, it is possible that the drug undergoes conversion to a vasodilator agent in the body. Dihydroergocornine is not adrenolytic in the usual intravenous dosage but possesses this property when given intra-arterially in high concentration.

In the usual intravenous dosage benzodioxane has no peripheral vasodilator action and is therefore not sympatholytic. Intra-arterially it has no direct vasodilator action and blocks epinephrine vasoconstriction only when injected intra-arterially in high concentrations.

OBSERVATIONS ON AIR SWALLOWING DURING OPERATIONS. *John L. Bell, M.D. and Walter C. Maddock, M.D., Chicago, Illinois.*

It is generally accepted that the main source of gas in abdominal distention is external air, and the way it is alleged to enter the alimentary canal is commonly suggested by the term "swallowed air." To learn more about swallowing during operations a series of twenty-three patients were observed.

A Levine tube was passed into the stomach and all gas was removed and measured. Swallowing movements during the induction of the anesthesia varied from 0 to 5. This is in great contrast to earlier work in which open ether was used and it is probably due to our rapid induction. No swallowing movements were observed during the operations.

The amounts of gas aspirated during operations under spinal-pentothal and inhalation anesthesia ranged from 0 to 130 cc., with an average of 73 cc. In one case 780 cc. were aspirated from the stomach during a period in which there was abnormal respiration due to the patient's tongue dropping back. With this obstructed airway, it is believed that air entered the esophagus rather than the trachea.

In five of ten cases in which curare was used to supplement the inhalant anesthetic some intercostal paralysis occurred, necessitating positive pressure to augment respirations. The amounts of gas aspirated in these cases varied from 300 cc. to 1,700 cc. With the exception of the five cases in which curare necessitated positive pressure anesthesia, the total volume of gas

aspirated during the operations would probably not contribute to postoperative abdominal distention.

RATIONALE OF THERAPY IN ACUTE VASCULAR OCCLUSIONS BASED ON MICROMETRIC OBSERVATIONS. *Harold Laufman, M.D., Wayne B. Martin, M.D. and Stanley W. Tuell, M.D. (Introduced by Howard A. Lindbergh, M.D.), Chicago, Illinois. (From the Department of Surgery, Northwestern University Medical School.)*

By means of a modified Kniseley fused quartz rod transillumination apparatus, actual micrometric measurements of small vessel caliber made it possible to evaluate the effects of certain therapeutic measures in acute vascular occlusions. All observations were made on mesenteric vessels in the dog. Much of the therapy in vogue today is controversial and there is confusion concerning the physiologic responses to vascular occlusions. It was necessary, therefore, to establish the typical patterns of response in small vessel caliber following occlusions. All occlusions were made using a rubber tipped clamp. Following main stem arterial occlusion, both the small artery and vein under observation diminished in caliber. After release of the occlusion a small artery remained in moderate spasm for a short period of time before returning to the control caliber. This phenomenon we termed residual vasospasm. Following main stem venous occlusion, the small veins became dilated while the small arteries exhibited a marked diminution of caliber. After release of a venous occlusion temporary residual spasm in the small artery was again noted. As the artery returned to its control caliber the engorged vein also regained its control diameter.

Alterations in the basic pattern as produced by certain therapeutic measures were then observed. Experiments with sympathectomized specimens indicate that the afferent and efferent fibers of both arteries and veins are largely responsible for the patterns of response following occlusions while the pressure gradient of blood flow through the vascular tree became important only when the spastic impulses were overcome by the intravascular pressure. Such a situation accounts for venous engorgement during venous occlusion in the presence of increased tonus in the vein wall. Regional sympathetic denervation eradicates the pattern

of small vessel spasm to an extent unequalled by vasodilators employed. Oxygen therapy was found to have no effect on vessel caliber. Papaverine hydrochloride was found to be of value in releasing some of the reflex arterial vasospasm in venous occlusions if used before thrombosis occurred. In arterial occlusions the drug was of value only when collateral arteries existed above the occlusion. Once an occlusion was released the drug was able to eradicate residual spasm in the small vessels. Tetraethylammonium chloride in non-shock-producing doses was able to counteract the vasospastic effects following acute venous occlusion in about 50 per cent of cases while in acute arterial occlusions it was without value unless there were collateral vessels present.

EFFECTIVENESS OF ANTICOAGULANT THERAPY AS OBSERVED IN 300 CASES. *Ivan F. Duff, M.D. (Introduced by W. D. Robinson, M.D.), Ann Arbor, Michigan.* (From the Department of Internal Medicine, University of Michigan.)

Among those given treatment were 133 patients with peripheral venous thrombosis, thirty-five with pulmonary embolism and twenty-seven with myocardial infarctions; seventy-four postoperative patients were treated prophylactically. One hundred thirteen received preliminary heparinization, the remainder received only dicumarol.

Dicumarol required about 2.7 days to effect therapeutic prothrombin concentrations (30 per

cent or less) which were maintained an average of ten days. Excessive hypoprothrombinemia occurred in 17 per cent of the patients. Dicumarol induced bleeding in 11.2 per cent of the subjects; this occurred in three-fifths of those who had prothrombin concentrations below 20 per cent. The incidence of minor and major bleeding was 61 per cent and 29 per cent, respectively; there was one fatality from hemorrhage. Heparin rarely induced bleeding.

One of the postoperative patients receiving prophylactic dicumarol developed thromboembolism at a low level of prothrombin. Satisfactory resolution of venous thromboses resulted in 90 per cent of the patients; this was accelerated by employing preliminary heparinization. In eight of these patients thromboembolism occurred or progressed at effective prothrombin levels.

All the patients (nineteen) with simple postoperative pulmonary embolism recovered. Five deaths occurred in the remaining sixteen patients with pulmonary embolism and infarction, the majority of whom had organic heart disease and had sustained their infarction before hospitalization. Anticoagulants were used with poor success in treating recurrent pulmonary emboli arising from mural thrombi.

Five (18.5 per cent) of the patients with myocardial infarctions died. Mural thrombi, present in two, were associated with recurrent pulmonary infarctions in one subject. Among those who lived secondary thromboembolism occurred in 11.1 per cent.

Case Report

Weber-Christian Disease*

RICHARD J. KENNEDY, M.D. and LOUIS R. MURPHY, M.D.
New York, New York *Seattle, Washington*

WEBER-CHRISTIAN disease, or relapsing, febrile, nodular non-suppurative panniculitis, has been regarded as a rare disease but is nevertheless of interest to both the internist and to the pathologist; to the former because of the

low grade fever, oropharyngeal infections, vague joint pains or manifest arthritis. Fever, ranging from 99° to 106.4°F., has been present in 87 per cent of the cases. The rise in temperature is gradual and coincides, as a rule, with the appearance of sub-

TABLE I
DISTRIBUTION OF PATIENTS ACCORDING TO AGE

Age	No. Patients
0-9	2
10-19	4
20-29	6
30-39	11
40-49	5
50-59	9
60-69	1

TABLE II
SITES INVOLVED IN THIRTY-EIGHT PATIENTS

Sites	No. of Patients
Thigh.....	28
Leg.....	25
Arm.....	24
Trunk.....	22
Buttock.....	2
Breast.....	2
Feet.....	1
Face.....	1

striking febrile reaction associated with minimal, localized pathologic changes and to the latter because of its histologic resemblance to many "nodular diseases."

The purpose of this paper is first, to review the clinical and pathologic findings in Weber-Christian disease in order to establish criteria for diagnosis; second, to review briefly the cases reported since 1944; third, to add three cases not previously reported and finally, to suggest a relationship between Weber-Christian disease and dermatomyositis.

Weber-Christian disease has been reported in every age group. (Table I.) The youngest patient was a twenty-three-month old male and the oldest a man of sixty-four. In the thirty-eight cases reported from 1892 to the present 71.8 per cent have occurred in females. Since 1944, 50 per cent of the cases have occurred in males.

The disease may be ushered in abruptly or preceded by indefinite prodromas for two to four weeks. The more common prodromal symptoms are general malaise,

cutaneous nodules or fever may not appear until softening of the nodules occurs. The subcutaneous nodules have varied in diameter from 1 to 12 cm. and in numbers from one to thirty. While the hands, face and feet are usually spared, nodules have appeared on all parts of the body and have been especially common on the thighs. (Table II.) In 78 per cent of the cases the nodules were tender but pain was a variable symptom.

The overlying skin may be red if the nodules are superficial. When involution begins, the skin becomes pigmented and atrophy occurs frequently (72 per cent of cases). In a few instances rupture of a nodule occurred without suppuration and a cloudy, yellow, fatty fluid was extruded. With one exception,¹ admittedly due to contamination, smear and culture of such fluid did not reveal bacteria.

Fever persists as long as new nodules appear and until those already present regress. The longest febrile period reported for a single relapse has been 115 days.

* From the Medical Division, St. Vincent's Hospital, New York, N. Y.
672 AMERICAN JOURNAL OF MEDICINE

Relapses are common and have recurred for as long as fifteen years. In three of the eight cases reported since 1944 splenomegaly has been noted.

Early in the course of the disease leukopenia is the rule with the leukocytes usually less than 7,000/cu. mm. (five of eight cases). The lowest count² found was 1,000/cu. mm., with moderate lymphocytosis. Baumgartner and Riva¹ noted that leukocytosis, with an increase in segmented forms, followed the initial leukopenia when involution and softening of the nodules occurred.

Although the clinical picture appears to be fairly constant, the pathologic findings are diverse. Some of the recent cases bear little resemblance to the original pathologic descriptions. Christian³ described the microscopic appearance of "cellular infiltration of the panniculus adiposus with at times extension into the fat of the adjacent layers. The cells are lymphocytes, plasma cells, a few polymorphonuclear leukocytes, endothelial cells phagocytic for fat droplets and fibroblasts in various admixtures. An occasional multinuclear giant cell is seen. Some areas show a granular appearance due to necrosis of cells and fat tissues." Spain and Foley,⁴ Friedman,⁵ Allen⁶ and Kritzer⁷ in their biopsies noted the infiltration to be composed mainly of lymphocytes and large mononuclears. Larkin et al.,⁸ Arnold⁹ and Zee¹⁰ on the other hand describe infiltration of the areas with polymorphonuclear and mononuclear cells with few lymphocytes present. We believe that the variation in the pathologic findings may be due to the difference in age of the nodules biopsied. Spain and Foley⁴ whose patient was autopsied divided the changes in the panniculus into three stages: In the earliest lesions small accumulations of fat-laden macrophages were noted. In larger lesions small central areas of fat necrosis were seen, about which were lymphocytes, polymorphonuclears and fat-laden macrophages. The older lesions showed a decrease in necrotic material and inflammatory cells were replaced by fibrous tissue.

There is a considerable difference of

opinion in regard to what are the characteristic changes in the interlobular fibrous septa. Christian did not describe them. Bailey's¹¹ view, generally accepted by American investigators, is that "a feature of panniculitis to be emphasized is the tendency for the interlobular connective tissue septa to retain the same width throughout. Edema, necrosis and infiltration may be present but extensive fibrosis, extending from the point where the larger vessels lie, is usually conspicuous by its absence. Thus it seems that the changes occur mainly as a result of lipophagic cells around the smaller blood vessels within the fat lobule." Allen⁶ states that the lesion in its typical form is characterized by infiltration of the fat lobules themselves rather than the septa. Baumgartner and Riva¹ describe inflammation and thickening of the connective tissue septa and note also an increase of the intralobular connective tissue. Septal immunity, emphasized by American observers, is an indefinite term that appears to mean absence of fibrosis in the perilobular areas rather than freedom of the septa from infiltration.

The condition of the blood vessels in the nodule is of prime interest for it would seem to furnish a clue to the pathogenesis of the lesion. Christian³ noted that the blood vessels were usually normal. A few showed periarteritis and rarely endarteritis with proliferation of the endothelial cells. Bailey¹¹ described obliteration of larger blood vessels and also noted in his third case obliteration of vessels within the fibrous septa. Cummins and Lever¹² in both of their cases described lamellation of the walls of the veins and subendothelial edema. Arnold⁹ noted extensive arteriolitis with thrombus formation and recanalization. Larkin⁸ noted small vessels surrounded by macrophages, lymphocytes and plasma cells. Zee¹⁰ described infiltration of the vessel walls by inflammatory cells and small hemorrhages into the adipose tissue. Friedman⁵ noted proliferation of the adventitia of vessels within the lesion. Shaffer¹³ has offered evidence, however, against primary vascular involvement

for in his patient there were widespread changes in the panniculus with softening and rupture of the nodules, but biopsy of a very early lesion showed only minimal perivascular inflammation.

Five patients with Weber-Christian disease have been autopsied. Kritzler's⁷ patient showed no striking changes in the internal fat deposits. A fatty liver with widespread central necrosis was found and the spleen was enlarged. Fat emboli were present in the lungs and many of the cells of the adrenal cortex had undergone hydropic degeneration. The case of Spain and Foley⁴ ran a course of eight days, terminating in uremia. Autopsy revealed chronic glomerulonephritis and Weber-Christian disease. In addition to subcutaneous fat necrosis there was necrosis of the pancreatic adipose tissue and of areas in the mesenteric, omental and peritracheal fat. Fatty changes were present in the liver. It has been doubted that Friedman's⁵ case should be considered one of Weber-Christian disease because the patient died of staphylococcus septicemia. The duration of the disease was five years with multiple subcutaneous nodules appearing during that time. That coagulase-positive *Staphylococcus aureus* was obtained from a terminal blood culture does not appear to us to influence the original diagnosis of Weber-Christian disease. It is impossible, however, to separate the postmortem findings due to the panniculitis from those due to terminal septicemia. The same is generally true of Ungar's¹⁴ case although he offered much less clinical evidence to substantiate a diagnosis of Weber-Christian disease. The latest autopsied case is that of Mostofi and Engleman¹⁵ whose patient died in a convulsive seizure seven months after onset of the disease. The liver showed fatty changes, especially in the peripheral cells; the mid-zonal and central areas were the sites of necrosis and hemorrhage; early proliferation of the bile ducts was noted. The pancreas revealed fatty and hydropic degeneration of the acinar cells. The peripancreatic and intralobar fat was infiltrated

with plasma cells, lymphocytes and phagocytes. The inflammatory reaction was closely related to the small arteries and veins. There also was considerable involvement of the peripelvic and peri-adrenal fat and of the epicardium. Widespread reticulo-endothelial hyperplasia was noted.

The most constant postmortem findings are non-specific fatty infiltration and necrosis in the liver. The changes in the internal fat deposits mimic those noted in the subcutaneous adipose tissue.

The cases reported since 1944 are summarized in Table III.

CASE REPORTS

CASE I. J. H., a sixty-three year old Belgian male, entered the hospital February 19, 1946, complaining of joint pains, fever and subcutaneous nodules of two weeks' duration.

At the age of seventeen the patient had an attack of polyarthritis that confined him to bed for six months. He was well until the age of thirty-three when he developed polyarthritis and subcutaneous nodules. That illness differed from the present only in that it was much less severe and less abrupt in its onset. Symptoms (at that time) continued intermittently for three years with exacerbations lasting for about a month, followed by remissions of from two to three months. From the age of thirty-six to the onset of the present illness he had been free from any similar complaints. System review revealed only a history of dyspnea on moderate exertion lasting for the past two years.

Physical examination revealed that the patient was an elderly white male who appeared both acutely and chronically ill. The temperature was 102.4°F., pulse 96 and respiration 22. The skin was warm, loose and dry, with evidence of moderate weight loss. The pharynx was acutely inflamed. The heart was slightly enlarged to percussion and the rhythm was regular with rare premature contractions. The heart sounds were of good quality with a blowing systolic murmur (grade III) at the apex. Blood pressure was 135/85. Both elbows were swollen, tender, red and hot. The shoulders and knees were tender and motion was limited because of pain. There were two raised, red, firm, non-tender nodules in the subcutaneous tissue apparently attached to the epidermis. The larger nodule (5 by 6 cm.) was on the posterior

TABLE III

Author	Age	Sex	Duration	Site	Temperature	White Blood Cells	Therapy	Findings
Kritzler*	34 yr.	F	29 mo.	Thighs; buttocks; arms	101–104°F.	?	?	Autopsy: Non-suppurative exudate in panniculus; collapse of many fat cells; necrosis of the exudate; lipophagocytosis and entry into the adipose cells of wandering phagocytes and lymphocytes, both in the exudate and within the adipose cells; no changes in internal fat deposits; spleen enlarged; liver fatty with widespread necrosis mostly centrally located; fat emboli in lungs; hydropic degeneration of adrenal cortical cells
Larkin	23 mo.	M	6 mo.	Thighs; ankles	102°F.	6,000; 54 per cent polymorphonuclears	?	Biopsy: Polymorphous cellular infiltration, many mononuclear phagocytes with vacuolated cytoplasm between the fat cells; small vessels surrounded by macrophages, lymphocytes and plasma cells
Spain and Foley	51 yr.	M	8 days	Arms; legs	99–104°F.	8,500; 85 per cent polymorphonuclears	?	Biopsy: Fat necrosis with surrounding infiltration of lymphocytes, occasional polymorphonuclears and fat-laden macrophages, moderate increase in fibrous tissue adjacent to lesion.
Ives	53 yr.	M	10 wk	Arms; thighs	101°F.	1,000–2,300; 59 per cent lymphocytes	Sulfathiazole Penicillin	Autopsy: Chronic glomerulonephritis; pancreatic fat necrosis; fatty changes in liver; necrotic nodules in mesenteric, omental and pre-tracheal fat Biopsy: None
Baumgartner and Riva	56 yr.	F	3 episodes in 8 yr	Whole body except head; hands; feet	99–102°F.	Early, 5,300; 43 per cent lymphocytes; later, 15,000; 87 per cent polymorphonuclears	?	Biopsy: Infiltration of panniculus by lymphocytes, fibroblasts, some plasma cells; later neutrophil, lipophages and giant cells; connective tissue septa thickened and infiltrated
Friedman	23 yr.	F	5 yr.	Legs; thighs; buttocks; breast	103–105.8°F.	1,700–2,500; 42–55 per cent polymorphonuclears	?	Biopsy: Chronic granulomatous inflammation predominantly involving subcutaneous fat lobules; infiltration with round cells and large mononuclears; proliferated lamellae of adventitial cells about some vessels; death due to Staphylococcus aureus, coagulase positive, septicemia
Arnold	27 yr.	F	17 mo.	Thigh; forearm	99°F	12,100; normal differential	Recovery attributed to sulfapyridine	Biopsy: Arteriolitis with thrombus formation and recanalization; round cell and polymorphonuclear infiltration and fibrous replacement of subcutaneous fat
Zee	23 yr.	M	1 mo.	Abdominal wall; arm; legs; back; trunk	104.0°F.	3,200; 50–75 per cent polymorphonuclears	Sulfadiazine ineffectual; temperature normal after 15 days of penicillin	Biopsy: Epidermis edematous; fascia and adipose tissue hemorrhagic; minimal infiltration about blood vessels and dermal appendages; coagulation necrosis of some fat lobules, others densely infiltrated with mononuclears and neutrophils; interlobular septum edematous; small round coccoid bodies with the appearance of bacteria found in some areas
Allen	48 yr.	F	?	Thighs	Low grade	?	?	Biopsy: Infiltration of monuclear cells, lymphocytes and histiocytes that select the fat lobules rather than the septa

* This case not summarized by Larkin.

TABLE III (Continued)

Author	Age	Sex	Duration	Site	Temperature	White Blood Cells	Therapy	Findings
Ungar.	37 yr.	F	9 mo.	Trunk; forearm; thighs	102–104°F.	18,000; moderate shift to the left	Potassium iodide produced flare-up	Biopsy: First, lipogranuloma; second, suppurative inflammation of adipose tissue Autopsy: acute diffuse, suppurative peritonitis due to <i>Streptococcus hemolyticus</i> ; relapsing and granulomatous inflammation of adipose tissue throughout the body predominantly in the retroperitoneal space; ulcer of skin due to extension of suppurative panniculitis to arterioles with subsequent thrombosis; thrombosis of pelvic and iliac veins and inferior vena cava
Mostofi and Engleman	38 yr.	M	9 mo.	Arms; legs; thighs; trunk; forehead	101–104°F.	2,600–5,000; 68 per cent polymorphonuclears	Atabrine, quinine, sulfonamides, emetine, penicillin and antimony, ineffectual	Biopsy: Thin and atrophic epidermis; pink-staining material precipitated inside some fat cells; collapse of the cell membrane of a majority of cells; ruptured cells invaded by foamy macrophages, lymphocytes, plasma cells and neutrophils; macrophages containing an occasional ingested lymphocyte and red blood cells seen; inflammatory reaction marked around small-sized vessels Autopsy: Bilateral blood-tinged pleural effusion; liver: fatty changes in peripheral cells, necrosis and hemorrhage in mid-zone and central areas; proliferation of bile ducts; considerable involvement of peripelvic, periadrenal and epicardial fat; widespread reticulo-endothelial hyperplasia

wall of the right thorax while the smaller (2 by 4 cm.) was on the medial aspect of the right knee. There were no other significant physical findings.

Laboratory data revealed the following: Hemoglobin, 15.6 Gm.; red blood cells, 5,120,000; white blood cells, 15,500; segmented forms, 65 per cent; band forms, 11 per cent; lymphocytes, 24 per cent. Urine: specific gravity, 1.012 to 1.015; albumin: trace. Blood chemistry: uric acid, 2.5 mg.; cholesterol, 233 mg.; sedimentation rate, 18 mm. in 25 minutes; cephalin flocculation, 1 plus in 48 hours. Agglutination for typhoid, paratyphoid A and B, typhus and brucella, negative. Blood culture, negative.

X-ray examination showed that soft tissue swelling was present in both elbow joints. Advanced osteo-arthritic changes of the productive type were present in the right knee with earlier changes in the left knee and in both hip joints.

The patient was hospitalized for sixty-seven days. He had recurrent episodes of fever as high as 105.2°F., accompanied by the appearance of

subcutaneous nodules, chiefly on the buttocks and lower extremities but also on the trunk and arms. Pain and swelling of the knees, elbows and shoulders accompanied some of the flare-ups. The longest continuous febrile period was eighteen days. Of the numerous nodules that appeared only one became fluctuant and on aspiration yielded 1.5 cc. of thin, yellow, cloudy fluid. No organisms were obtained on smear or culture of this fluid. During the hospital stay there was a slight decrease in hemoglobin and red cells. Leukocytosis persisted without any change in the differential count. The sedimentation rate remained accelerated. As the nodules subsided there was dimpling of the skin and in some spots brownish pigmentation appeared over the site of the nodules.

Two courses of intramuscular penicillin were given, each for a period of four days for a total of one million units. Salicylates were given orally and rectally in large doses. Neither form of therapy seemed to have any influence on the course of the disease.

A specimen was taken from the right buttock, consisting of skin and subcutaneous tissue, and

a biopsy was performed. The epidermis was intact and showed no changes. There was some edema and slight cellular infiltration of the deeper layers of the derma. No changes were noted in the hair follicles, sweat or sebaceous glands. The septa between the fat lobules were edematous and infiltrated with many cells, chiefly large mononuclears with dark-staining nuclei and granular cytoplasm but also with lymphocytes and polynuclears. (Fig. 1.) There was extensive necrosis of fat cells with evidence of fat being phagocytosed. (Fig. 2.) In addition to the cells described previously large mononuclears with pale nuclei (foam cells) and giant cells were present in close approximation to the necrotic fat. Polymorphonuclear leukocytes were more frequent in areas showing severe necrosis. Mild to moderate perivascular infiltration was noted and there were a few small hemorrhages.

CASE II. D. A., a fifty-eight year old white female, was admitted to the hospital complaining of nausea and vomiting of one week's duration, accompanied by constant, moderately severe pain in the right upper quadrant. There was a past history of intolerance to fatty foods and of several attacks of abdominal pain and vomiting that had been attributed to gallbladder disease.

Physical examination showed that the patient was a moderately obese woman; temperature was 106.2°F. and pulse 120. Blood pressure was 160/100. There was moderate tenderness in the right upper quadrant. The examination was otherwise negative.

The outstanding feature of the laboratory studies was failure of the leukocytes to rise above 9,000 cu. mm. although a moderate shift to the left was noted. The blood Kahn was negative. The urine showed a persistent trace of albumin.

A flat plate of the abdomen in the prone and erect positions revealed slight elevation of the right dome of the diaphragm. The heart was moderately enlarged and the lungs showed increased fibrosis in the roots and bases. The gallbladder was not outlined by the administration of oral dye.

The patient was given 670,000 units of penicillin intramuscularly for a period of seven days. Abdominal signs and symptoms disappeared by the fourth day. By the sixth day the temperature had gradually fallen to 101°F. and remained at that level for eighteen days, during

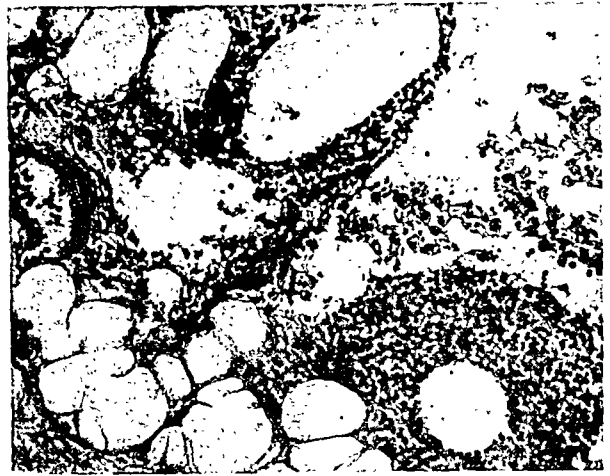


FIG. 1. Case I. Section of panniculus showing marked cellular infiltration of the septa. ($\times 100$.)

which time subcutaneous nodules appeared on the thighs and arms.

A biopsy specimen consisted of subcutaneous tissue. The interlobular fat septa were infiltrated with a great many cells, lymphocytes predominating. (Fig. 3.) Fibroblasts were increased, and there appeared to be proliferation of fibrous tissue in the septa. Fat necrosis was marked. Vacuolated giant and foam cells were present in great numbers. There was a paucity of blood vessels in the areas of fat necrosis and mild perivascular infiltration was the only change noted.

CASE III. R. E. A., a sixty-three year old widow was admitted to the hospital in October 1943, in a stuporous condition. A week prior to admission, while walking, she suddenly lost the power in her legs and fell to the ground without losing consciousness. Since then, she noticed residual weakness in her legs.

The patient had had two previous admissions to this hospital. In 1941 a diaphragmatic hernia that reduced itself when the patient assumed an upright position was demonstrated. In 1943 repair of the diaphragmatic hernia gave her complete relief from periods of abdominal pain, nausea and anorexia. Physical examination revealed evidence of right facial paralysis, a temperature of 101°F. and many scattered subcutaneous nodules of which the patient had been unaware. The nodules were present on the extensor surfaces of the legs, on the medial and lateral aspect of the thighs, over the right elbow and the right arm and left forearm. The nodules were not tender and with the exception of the largest, which appeared to be fluctuant, were

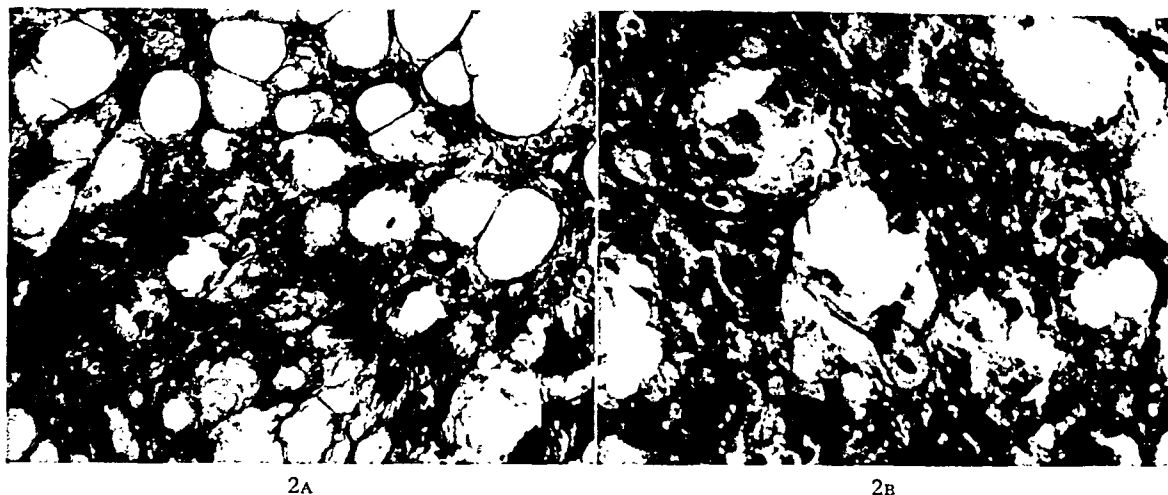


FIG. 2. Case I. A, section of panniculus; extreme fat necrosis. Many large mononuclear cells with foamy cytoplasm present in necrotic areas and between fat cells. ($\times 100$.) B, ($\times 250$).

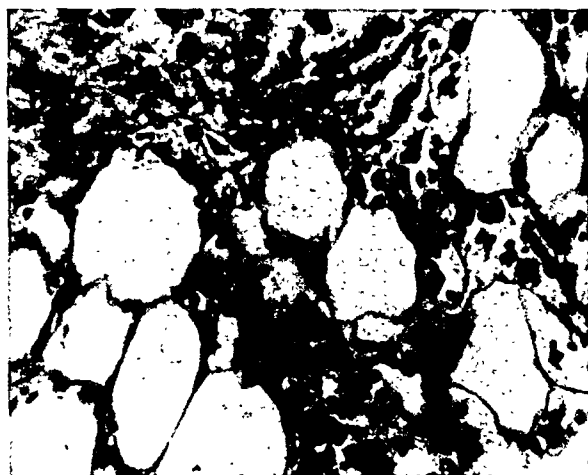


FIG. 3. Case II. Section of panniculus. Infiltration of the septa with lymphocytes; rare giant cell present. Increase of fibrous tissue in the septa. ($\times 200$.)

firm. The overlying skin was reddened. The diagnosis at admittance was erythema nodosum.

Laboratory data was as follows: Red blood cells, 4,010,000; hemoglobin, 80 per cent; white blood cells, 13,000; polymorphonuclears, 76 per cent; lymphocytes, 21 per cent; monocytes, 2 per cent; eosinophiles, 1 per cent. Urine: 2 plus albumin and 10 to 12 white blood cells per high powered field.

Fluoroscopic examination of the chest showed enlargement of the left ventricle with moderate dilatation of the descending aorta. There was slight dilatation of the lower end of the esophagus and two small diverticula were found in this area.

The patients' temperature was 101°F. for the first forty-eight hours; it rose to 104.4°F. on the third day and gradually fell to 100°F. during the

next forty-eight hours. For the following six weeks, during which time the nodules gradually disappeared, the temperature fluctuated between 98° and 100.2°F.

The patient was seen in consultation by the Dermatological Service which suggested the possibility of Weber-Christian disease. All symptoms gradually subsided and the patient was discharged on the seventy-second hospital day. No therapy was given.

The biopsy specimen consisted of skin and subcutaneous tissue. No abnormalities were noted in the former. The inflammatory process appeared to be more acute in this specimen than in either of the previous specimens and there was little if any fibroblastic proliferation. The interlobular septa were heavily infiltrated with lymphocytes and polymorphonuclears and these cells were also common in areas of fat necrosis. Multinucleated giant cells were very conspicuous and various stages in the breakdown of fat were demonstrated. (Fig. 4.) The blood vessels showed endothelial proliferation, thickening of the walls and extensive perivascular infiltration with lymphocytes predominating. There were several minute hemorrhages.

Twenty-two months later the patient was re-admitted to one of the surgical services because of a painful mass of one week's duration over the lateral surface of the right knee. She stated that since her previous admission she had had many of these painful areas which persisted for about a month.

Physical examination at this time showed that generally there were no changes since the previous admission. Her temperature was

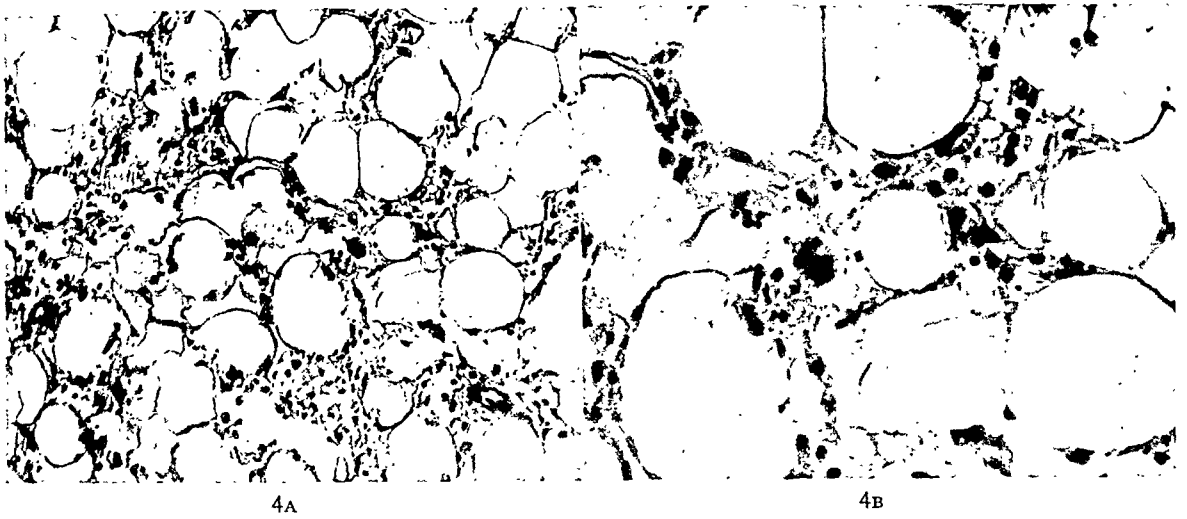


FIG. 4. Case III. A, section of panniculus. Minimal fibroblastic proliferation. Various stages in the breakdown of fat are present with destruction of cellular boundaries and phagocytosis of fat. ($\times 100$.) B, ($\times 400$).

101.6°F. Over the lateral aspect of the head of the right fibula there was a red, hot mass 3 cm. in diameter in the center of which was a red punctate area with a surrounding zone of erythema about 11 cm. in diameter. The temperature rose to 102.0°F. for twelve days and then in a period of two weeks fell to normal. During this time the mass resolved without fluctuation. The patient was given 6 Gm. of sulfadiazine daily for twelve days.

The patient was again seen in June, 1947 and there had been no recurrence of the nodules. No evidence of atrophy was present.

COMMENT

Relapsing, febrile, nodular, non-suppurative panniculitis is a well defined clinical entity and even in the absence of palpable nodules should be considered as a possible cause of unexplained fever since the early febrile stage, noted in some cases without palpable subcutaneous nodules, may well be due to panniculitis of the internal fat deposits.

No single factor has been advanced to explain the etiology of Weber-Christian disease. Weber¹⁶ doubts that the condition can be considered a pathologic entity. His case and two of Bailey's¹¹ were manifestly due to the administration of iodides. Ungar's¹⁴ patient had a flare-up following potassium iodide. Weber¹⁶ states that iodides are capable of producing the pathologic picture in certain susceptible

individuals. Similar pathologic changes have been produced by local application of cold, by subcutaneous injections and by trauma in established cases. In no instance has direct bacterial action been demonstrated as a cause of the lesions. The small coccoid bodies noted by Zee¹⁰ were not identified. The gram-negative rod recovered by Baumgartner and Riva¹ from a nodule produced necrotic hepatitis and lobular hemorrhagic pneumonia in mice but failed to agglutinate with the patient's serum. Ungar¹⁴ believes that failure to destroy the septum is against direct bacterial invasion.

It appears to us that the changes in the panniculus are secondary to disturbance in the vascular supply to the tissue. This seems to be the only manner in which the widely scattered localization of the inflammation can be explained. The incidence of the lesions on the extremities would seem to be due to the susceptibility of these parts to accidental trauma and to the predilection for vascular lesions to develop on dependent parts. We believe that the reaction in the adipose tissue is due to small areas of ischemia secondary to thrombosis or endarteritis in the smaller vessels, with subsequent death of the fat cells and ingestion of fat by macrophages and mononuclear elements. This explanation would seem to be excluded by the report of Shaffer¹³ in whose patient no changes were found in the

blood vessels. That case, however, is not typical of Weber-Christian disease, in that most of the lesions went on to liquefaction, a termination rare in relapsing, febrile, nodular, non-suppurative panniculitis.

The association of severe muscular and joint pain in our first patient with concurrent attacks of panniculitis brings to mind a question by Weber and Gray.¹⁷ "It is a question whether there may not be minor (incomplete) forms of dermatomyositis in which (in the absence of direct examination) the muscles appear to be not or only very slightly affected, and in which consequently a diagnosis of multiple relapsing panniculitis has to be made."

Meakins¹⁸ also states that where fibrositis, panniculitis and myositis begin and end, or whether they are all part of a local lesion, is difficult to determine. These are important points for further investigation for we have been able to find in the literature only a single description of muscle tissue taken in conjunction with the panniculus at biopsy. Conversely, in Weber and Gray's¹⁷ case of polydermatomyositis no mention is made of histologic change in muscle while extensively illustrated descriptions of the changes in the panniculus, considered classical of Weber-Christian disease, are given.

Whether Weber-Christian disease is limited to the panniculus remains to be demonstrated by more extensive biopsy and microscopic study.

SUMMARY

1. The literature on Weber-Christian disease is reviewed.
2. Three additional cases are reported.
3. A vascular disturbance is suggested as a cause of the reaction in the panniculus.
4. A relationship of relapsing, febrile, nodular, non-suppurative panniculitis to dermatomyositis is suggested.

REFERENCES

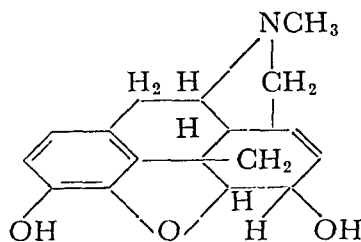
1. BAUMGARTNER, W. and RIVA, G. Nodular inflammation of adipose tissue. *Helvet. med. acta*, 12: 3-69, 1945.
2. IVEs, G. Relapsing febrile nodular non-suppurative panniculitis (Weber-Christian disease) with report of a case. *J. Missouri M. A.*, 42: 409-410, 1945.
3. CHRISTIAN, H. A. Relapsing febrile nodular non-suppurative panniculitis. *Arch. Int. Med.*, 42: 338-351, 1928.
4. SPAIN, D. M. and FOLEY, J. M. Nonsuppurative nodular panniculitis (Weber-Christian disease). *Am. J. Path.*, 20: 783-787, 1944.
5. FRIEDMAN, N. B. Fatal panniculitis (including autopsy). *Arch. Path.*, 32: 42-46, 1945.
6. ALLEN, A. C. Summary discussion conference on dermatologic pathology. New York State Association Public Health Laboratories, Case 123, 30-31, May 16, 1946.
7. KRITZLER, R. A case of Weber-Christian disease. *Proc. N. Y. Path. Soc.*, 47: 1940-1941.
8. LARKIN, U DE P, DE SANCTIS, A. G. and MARGULIS, A. E. Relapsing febrile nodular non-suppurative panniculitis (Weber-Christian disease); review of literature, with report of case. *Am. J. Dis. Child.*, 67: 120-125, 1944.
9. ARNOLD, H. L., JR. Nodular non-suppurative panniculitis (Weber-Christian disease); preliminary report of case controlled by sulfapyridine (sulfonamide). *Arch. Dermat. & Syph.*, 51: 94-99, 1945.
10. ZEE, M. L. Nodular non-suppurative panniculitis treated with penicillin. *J. A. M. A.*, 130: 1219-1220, 1946.
11. BAILEY, R. J. Relapsing febrile nodular non-suppurative panniculitis (Weber-Christian disease). *J. A. M. A.*, 109: 1419-1425, 1937.
12. CUMMINS, L. J. and LEUER, W. F. Relapsing febrile nodular non-suppurative panniculitis (Weber-Christian disease). *Arch. Dermat. & Syph.*, 3: 415-426, 1938.
13. SHAFFER, B. Liquefying nodular panniculitis. *Arch. Dermat. & Syph.*, 38: 535-544, 1938.
14. UNGAR, H. Relapsing febrile nodular inflammation of adipose tissue (Weber-Christian syndrome). Report of a case with autopsy. *J. Path. & Bact.*, 58: 175, 1946.
15. MOSTOFI, F. K. and ENGLEMAN, E. Fatal relapsing febrile non-suppurative panniculitis. *Arch. Path.*, 43: 417-426, 1947.
16. WEBER, F. P. A case of relapsing non-suppurative nodular panniculitis showing phagocytosis of subcutaneous fat cells by macrophages. *Brit. J. Dermat.*, 37: 301-311, 1925.
17. WEBER, F. P. and GRAY, A. M. H. Chronic relapsing polydermatomyositis with predominant involvement of the subcutaneous fat (panniculitis). *Brit. J. Dermat.*, 36: 544-560, 1924.
18. MEAKINS, J. C. The Practice of Medicine, 3rd ed., pg. 1141. St. Louis, 1940. The C. V. Mosby Co.

Editorial

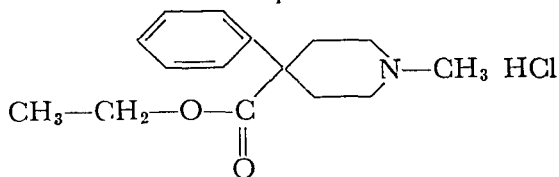
Synthetic Analgesic Drugs

FEW drugs have as impressive a history as opium. It has been used for more than two millenia although its important therapeutic applications were not generally recognized until more recently. The isolation of the principal alkaloids of opium in the nineteenth century and the more recent chemical modification of alkaloidal structure to produce substances such as dihydromorphinone (Dilaudid) and methyldihydromorphinone (metopon) represented important steps forward but did not foretell great progress in the search for analgesic drugs which could replace morphine or its related alkaloids.

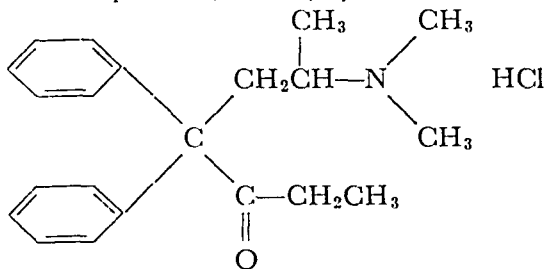
Only a decade has passed since the announcement of Eisleb and Schaumann that a relatively simple compound, meperidine (Demerol, Dolantin), an ester of phenylpiperidinecarboxylic acid, is a potent analgesic drug. This discovery proved that the structural peculiarities of the alkaloids of the morphine group need not dominate the search for new analgesics. It promised new insight into the relationship between chemical structure on the one hand, and analgesic potency, undesired toxic effects and addiction-liability on the other. This promise has been strengthened by the recent introduction of methadone. Methadone (amidon, Dolophine, Adanon) is a synthetic analgesic as potent as morphine. A derivative of heptanone, its structure differs from that of meperidine. The formulas here given enable one to compare the structures of morphine, meperidine and methadone.



Morphine



Ethyl-1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride. Meperidine (Demerol) hydrochloride.



6-Dimethyl-amino-4,4-diphenyl-heptanone-3 hydrochloride. Methadone (Dolophine, Adanon) hydrochloride.

Drugs used for a specific effect often have similar patterns of action extending to effects which either are undesired or undesirable or both. How similar are the pharmacologic patterns of morphine, meperidine and methadone? All three relieve pain and the analgesic action is the primary therapeutic use to which they are put. Meperidine is about one-tenth as potent as the other two in terms of the dose required for analgesia. Specialized experimental algesimetric tests suggested that methadone is even more

potent than morphine. However, clinical comparisons have not consistently revealed important differences in dose and for practical purposes morphine and methadone can be regarded as equipotent analgesics.

Is the liability to addiction with physical dependence and tolerance-development necessarily a part of the pharmacologic pattern of a potent analgesic drug? The evidence available requires an affirmative answer to this question although that answer must be provisional and subject to qualification. Himmelsbach, Isbell and their colleagues have studied in addicts as quantitatively as possible the phenomena of addiction to morphine and of physical dependence on the drug as measured by signs and symptoms of withdrawal. The addiction-liability of morphine with the development of unusual tolerance is notoriously high and there is a correspondingly great physical dependence on the drug. If morphine be used as a standard of addiction, then meperidine can be considered an analgesic of low addiction-liability. Primary habituation and addiction to meperidine have occurred but the number of such cases in psychiatrically normal persons is certainly small. On the other hand, it is a dangerous but less desired substitute for morphine in the real or potential morphine-addict and appears to resemble codeine in this respect. Tolerance of the analgesic or toxic effects of meperidine appears slowly and is much lower than that reached after repeated doses of morphine.

Apart from its analgesic action, the best evidence that methadone is a pharmacologic relative of morphine comes from studies of its effects in addicts. It can provide a euphoria nearly as satisfying as that of morphine and Anslinger has warned that addicts are often successful in obtaining the drug from physicians who would be suspicious of a request for morphine. It can be substituted for morphine without recognition by the addict. In fact, its substitution for morphine followed by abrupt withdrawal is probably the best means of withdrawing morphine since the abstinence

syndrome after methadone is much milder than after morphine alone (Isbell and others). Therefore, physical dependence, measured by abstinence symptoms, is much lower than for morphine even after doses of methadone approaching the limits of tolerance. If one were limited only to these considerations, he might conclude that the addiction-liability of methadone is considerable. Such a generalization may approach the truth in the real or potential addict but at present cannot be sustained from clinical experience in normal patients. There has been no report of primary addiction to methadone. In experimental animals, especially dogs, varying degrees of addiction with tolerance have been produced. On the other hand, in the monkey from which any data obtained should be more significant, Seevers and his colleagues could demonstrate addiction and tolerance-development for morphine but not for methadone. Normal patients requiring a drug for the relief of severe pain have taken methadone for weeks or even months. Tolerance may or may not appear and require a moderate increase of dose. Primary addiction with withdrawal symptoms has not been reported.

It would be expected that habituation and addiction would be facilitated by an analgesic causing euphoria. The euphoria which is commonly observed in patients receiving therapeutic doses of morphine occurs infrequently after meperidine (less than 10 per cent of patients) and perhaps even less often after methadone. Sedation is unquestionably much more pronounced after morphine than after meperidine or methadone. Indeed, the sedative action of methadone is usually so slight as to make it less suitable than morphine for special uses such as pre-anesthetic medication from which sedation may be desired. Cough can be efficiently suppressed by small doses of methadone whereas after meperidine an antitussive effect is not observed. The effects of the three drugs on smooth muscle offer interesting similarities and contrasts. Morphine reduces the propulsive activity of the

gastrointestinal tract by complex effects; it causes smooth muscle spasm especially of the sphincters; it lessens the secretion of digestive glands; its central action interferes with the defecation reflex. Although thought to be a spasmolytic drug, meperidine in normal persons usually increases smooth muscle tone, particularly of the small intestine. Neither meperidine nor methadone causes constipation. The spasmogenic action of meperidine is also illustrated by its action on the sphincter of the common bile duct which is thrown into spasm so that the intrabiliary pressure rises. Morphine and codeine act similarly. Morphine causes ureteral spasm whereas the effect of meperidine, if any, is to relax the smooth muscle of the ureters. At least in the anesthetized dog the injection of methadone is followed by relaxation of the ureters.

A comparison of the toxic effects of doses in the therapeutic range does not favor morphine. Dizziness, nausea and vomiting may follow the administration of any of the three analgesics. The frequency of these signs and symptoms, especially reported in ambulatory patients, is probably as high after morphine as after either meperidine or methadone. Minor toxic symptoms may be more characteristic of a particular drug. For example, pruritus is more common after morphine; flushing, perspiration and dryness of the mouth are more frequent after meperidine. Lethal doses of any of the three drugs cause respiratory paralysis. However, effects of therapeutic doses on respiration can usually be demonstrated only after morphine. Exceptional are patients with

intracranial lesions in whom meperidine may cause an alarming respiratory depression. In contrast, meperidine is the best available potent analgesic for obstetric use. Unlike either morphine or methadone it does not cause serious depression of respiration in the newborn infant. Toxic doses of all three analgesics cause mixed signs of central depression and excitation. Diffuse excitation rather than depression is more characteristic of meperidine than of morphine or methadone.

A comparison of morphine with its synthetic competitors, meperidine and methadone, demonstrates that either or both substitutes can usually replace it as a powerful and reasonably specific analgesic. The discovery of these synthetic analgesics, differing in structure from each other and from morphine, has greatly stimulated the investigation of related compounds, some of which have remarkable pharmacologic properties which are not necessarily desirable therapeutically. The therapeutic value of meperidine and methadone justifies an unrelenting search for better analgesics which may also be found, by trial and error, in compounds not suspected of possessing analgesic properties. Perhaps the ideal analgesic drug, specific for the relief of pain, useful for long periods without increase of dose or danger of habituation or addiction and causing few or trivial toxic effects can be discovered.

H. B. VAN DYKE, M.D.
Columbia University College
of Physicians and Surgeons,
New York, N. Y.

Modification of the Effects of Immobilization upon Metabolic and Physiologic Functions of Normal Men by the Use of an Oscillating Bed*

G. DONALD WHEDON, M.D., JOHN E. DEITRICK, M.D. and EPHRAIM SHORR, M.D.
with the technical assistance of

V. TOSCANI, V. BUNIAK DAVIS and E. STEVENS
New York, New York

THE effect of immobilization upon various metabolic and physiologic functions of four normal young men has been the subject of a previous communication.¹ The results of this study revealed that immobilization over periods of several weeks brought about significant losses of nitrogen, sulfur, calcium, phosphorus and potassium in healthy men. Creatine metabolism, control of the circulation in the upright position, and muscle mass and strength were also significantly impaired. These findings provided a quantitative measure of the degree to which immobilization *per se* may contribute to the metabolic and circulatory derangements observed in traumatic and infectious states.

There has been a rapidly growing interest in recent years in the development of methods for shortening convalescence. These methods have included early ambulation for postoperative patients²⁻⁵ and programs of physical reconditioning inaugurated during the war by the British⁶ and later adopted by our own military forces.⁷⁻¹⁰ These methods are not generally applicable to all

disease states or to all types of patients; they are primarily designed for convalescence after brief illness and for patients whose physical condition is such as to permit ambulant activity during convalescence. All these programs allow for a variable period of inactivity after the infectious, surgical or traumatic episode prior to the institution of rehabilitating procedures

The present study was primarily concerned with the development of procedures which could be instituted without delay and which would be applicable to conditions necessitating prolonged immobilization and for which convalescent training methods are unsuitable. These represent an important group of diseases, such as spinal cord injury, fracture of the pelvis or spine, severe burns and abdominal wounds, and extensive paralysis resulting from poliomyelitis or cerebral vascular accidents. Prolonged immobilization exposes these patients not only to derangements of circulatory, muscular and metabolic functions but also to the dangers of stone formation in the urinary tract and its consequences. The

* From the Department of Medicine, Cornell University Medical College, the New York Hospital and the Russell Sage Institute of Pathology, New York, N. Y. This investigation was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University Medical College, and was aided in part by a grant from the National Foundation for Infantile Paralysis, Inc.

desirability of any procedure which would maintain the body in the best possible metabolic and physiologic state during the period of enforced immobilization is evident.

Among the methods considered were calisthenic exercises, massage and passive exercise. These were quite unsuitable for the specific experimental conditions being explored which required that the lower half of the subjects' bodies be encased in plaster, as in the previous study, which was to serve as the base-line for the evaluation of the therapeutic regimen. The extent of the circulatory derangements observed during immobilization in the previous study suggested that benefit might be derived from any device, such as the oscillating bed described by Sanders¹¹ which would bring about continuous postural changes. It was conceivable that this bed, which rocks slowly back and forth, raising the head and lowering the feet with each oscillation, might exert favorable effects upon the circulation and possibly upon metabolic functions. This bed had the further advantage of being applicable to patients immobilized in plaster. Finally, any gain achieved by use of the bed would conserve nursing and physiotherapy facilities. For these reasons, the Sanders oscillating bed was selected for evaluation of its possible beneficial effects on the variety of physiologic and metabolic effects previously observed to follow immobilization in an ordinary hospital or fixed bed.

PROCEDURE

Three normal healthy young men were studied on a constant dietary intake before, during and following a five-week period of immobilization in plaster casts in oscillating beds. The three subjects had all taken part in the immobilization experiment (on standard hospital or fixed beds) previously reported.¹ The metabolic and physiologic data of each subject in the fixed bed experiment could therefore serve as the control for his data in the present experiment since the same experimental conditions were maintained, except for the use of oscillating beds during the immobilization period. Identical metabolic balances and physi-

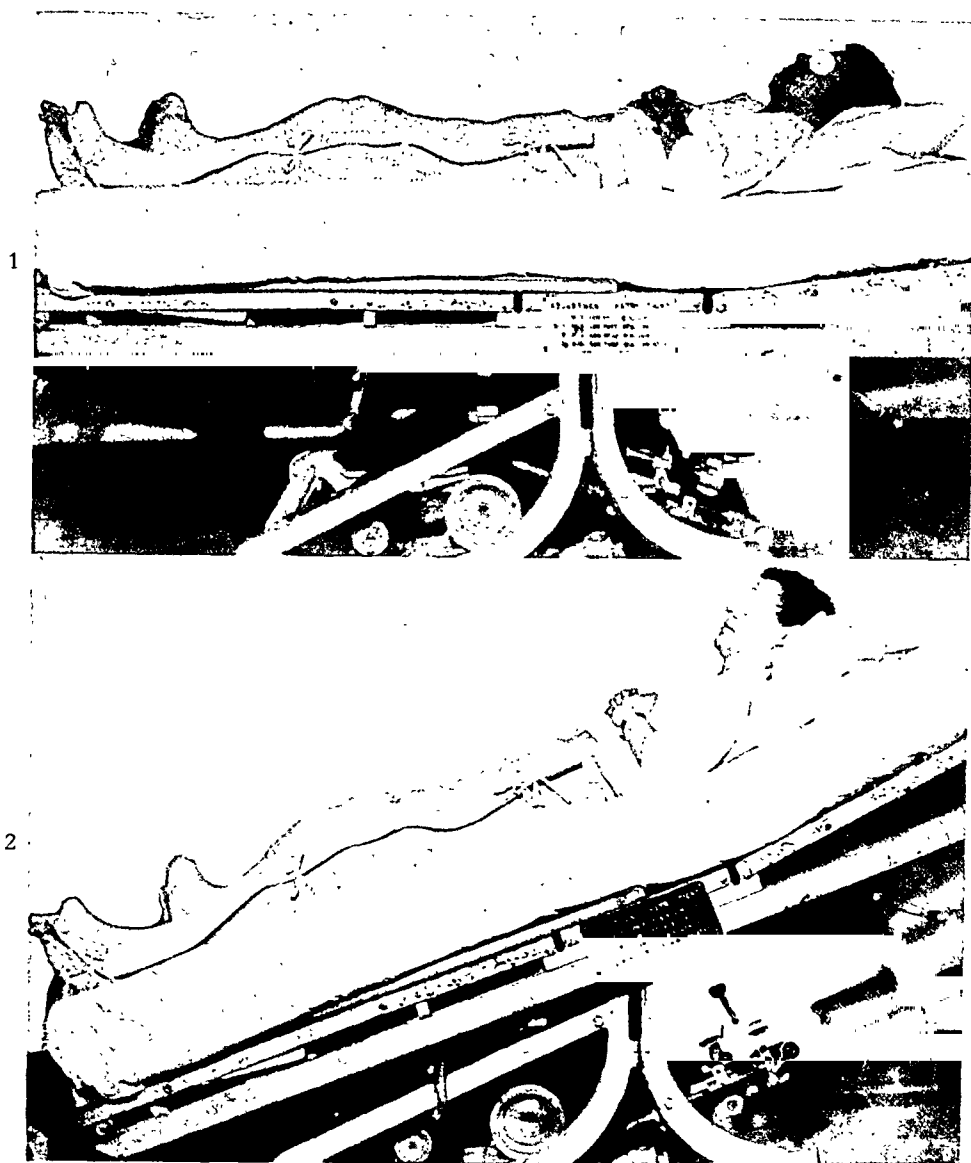
ologic studies were carried out on the Metabolism Ward of the New York Hospital and the Russell Sage Institute of Pathology.

During the control phase of the experiment, which lasted four to five and one-half weeks, the subjects carried on the same degree of activity as in the control phase of the fixed bed experiment. In addition to being up and about on the Metabolism Ward, they took exercise in the form of calisthenics for one-half hour, swimming for one-half hour each day and one hour walks outside the hospital under escort three or four times a week.

During the immobilization period, which lasted five weeks, the subjects were placed in the same type of cast as in the fixed bed experiment, a bivalved plaster cast extending from the umbilicus to the toes. Time out of the casts for bowel movements and for tilt table and ergometer tests was the same as in the fixed bed experiment and averaged thirty to forty minutes daily.

For subjects E. M. and C. O. the oscillating bed was in motion altogether eight hours daily. For subject S. W. the oscillating bed was in motion twenty-one hours daily, being stopped only for meals, bed baths and bowel movements. The beds rocked slowly up and down on a fulcrum at the middle of the bed (Figs. 1 and 2); the total arc of excursion was 24 degrees, the feet moving 5 degrees above and 19 degrees below the horizontal. The speed of oscillation was adjusted so that one complete cycle required one and three-fourths minutes. The subjects became adjusted to the motion of the bed within two days. The bed rocked so slowly that they were barely conscious of movement and were merely aware of a slight shift of weight with each oscillation and slight pressure chiefly on the bottom of the heels in the foot-down position. The pressure on the heels initially provoked some soreness and redness which was eliminated by adjustment of the padding of the cast.

During the recovery period the subjects were allowed to be progressively ambulant on the third day and by the twelfth day resumed the same level of activity as during the control period. In subjects E. M. and C. O. recovery was studied for five weeks. In S. W. recovery was studied for six and one-half weeks following which he was again immobilized for a two-week period, this time in a *fixed* bed. The re-immobilization of this subject in a fixed bed was carried



Figs. 1 and 2. Subject in bi-valved plaster cast on oscillating bed, showing arc of excursion employed. One complete cycle required one and three-fourths minutes. Figure 1, head of bed down 5 degrees. Figure 2, foot of bed down 19 degrees.

out for the purpose of providing a check on the results of the first fixed bed experiment. Would the same healthy young individual respond to immobilization in a fixed bed in the same way and to the same degree as he had one year previously? The recovery phase following the two weeks' re-immobilization of S. W. was studied for eleven days.

Subjects E. M. and C. O. were studied in the oscillating bed experiment from September to December, 1945, during the same months of the year but one year later than they had been studied in the fixed bed experiment. Subject S. W. was studied from February to January,

1946, exactly one year after he had been studied in the fixed bed experiment.

SUBJECTS

The subjects, E. M., C. O. and S. W., ranging in age from twenty-one to thirty years, were described in the report of the fixed bed experiment.¹ The subjects' heights and weights are shown in Table I.

DIETS

Throughout the experiment all three subjects received a 2,800 calorie diet, the composition of which is given in Table I. In the previous fixed

bed experiment C. O. and S. W. had received this same diet whereas E. M. had received a diet of slightly lower caloric (2,500) and mineral content. A description of the diets and of their composition as determined by direct analyses

modification of the method of Herbert; in addition, heparin tolerance tests as outlined by de Takats¹⁵ and prothrombin time determinations by the Link-Shapiro method¹⁶ were carried out on S. W.

TABLE I
DAILY DIETARY INTAKE AND PHYSICAL CHARACTERISTICS OF SUBJECTS

Subject	Age Yr.	Height Cm.	Weight Kg.	Calories	Protein Gm.	Fat Gm.	CHO Gm.	Ca Gm.	P Gm.	Na Gm.	K Gm.
E. M.	30	177	72	2800	90	114	352	0.920	1.64	4.00	3.76
C. O.	21	180	66	2800	90	114	352	0.920	1.64	4.00	3.76
S. W.	21	181	66	2800	90	114	352	0.920	1.64	4.00	3.76

were given in the previous study¹ and in greater detail in separate reports.^{12,13} Sodium intake was kept constant at 4.0 Gm. per day for all subjects in this experiment. In S. W. the slight increase in nitrogen, calcium and phosphorus intake beginning at period VIII occurred because of the necessity for using the wartime "emergency" bread made from dark flour.*

METHODS

A. Chemical Studies. The metabolic balances (in seven-day periods), collection and preparation of specimens and methods of chemical analyses were carried out in the same manner as in the fixed bed experiment.¹ Urinary calcium, phosphorus and citric acid¹⁴ were determined on consecutive four- and three-day pooled specimens.

B. Physiologic Studies. Physiologic studies were carried out as described in the report of the fixed bed experiment with the following modifications. In all subjects, measurements of the girth of the legs were made with the device previously described¹ which involves the use of a wide metal band encircling the leg under constant and equal tension. With this device measurements of the circumference of the calves could be closely checked by different observers (standard deviation for four control weeks among all subjects = ± 2.4 mm., or 0.67 per cent). Blood coagulation studies included the determination of coagulation time by the Lee-White method and prothrombin time by a

RESULTS

A. Chemical Studies. 1. Nitrogen: During the control periods the subjects maintained small positive nitrogen balances with the output relatively constant. The average of the total outputs of the last three control periods served as the control base-line. Displacements or variations from the control base-line were employed for the calculation of the total losses of nitrogen occurring during immobilization on the oscillating bed and in the single re-immobilization in the fixed bed (subject S. W.). Calculation of the total losses occurring during immobilization in the first fixed bed experiment, with which these losses will be compared, were made in the same manner.

During the first four days of immobilization there was little change in nitrogen output. A rise then occurred which began on the fifth or sixth day and reached its maximum during the second and third weeks. In comparison with the fixed bed experiment the pattern of nitrogen loss was similar but the extent of nitrogen loss was approximately one-half as great in two of the three subjects. In the third subject (C. O.), whose losses of nitrogen were small in both experiments, the losses were almost identical in both types of immobilization. The repetition of immobilization of subject S. W. in the fixed bed (for two weeks) resulted in a loss of nitrogen identical with

*The authors are deeply indebted to Elizabeth Curtin, head nurse of the Metabolism Ward, for the supervision of the dietary and other aspects of the "patient" care during this and the previous immobilization study.

the loss sustained during the same period of time in the first fixed bed experiment and approximately twice as great as during the initial two weeks in the oscillating bed.

During the recovery phase the subjects

tion of nitrogen occurred at the fifth week for E. M. and C. O., at the second week for S. W.

A more detailed comparison of the changes in nitrogen metabolism in the fixed

TABLE II
COMPARISON OF NITROGEN METABOLISM DURING AND FOLLOWING FIVE WEEKS' IMMOBILIZATION IN FIXED AND OSCILLATING BEDS*
I. IMMOBILIZATION

Subject	Control	Five-week Period of Immobilization						Maximum Deviation from Control Base-line	
	Average Daily Balance Gm.	Average Daily Balance Gm.	Average Daily Loss Gm.	Total N Loss, First 2 Weeks Gm.	Total N Loss, First 3 Weeks Gm.	Total N Loss, 5 Weeks Gm.	Week of Occurrence	Deviation Gm./day (for that week)	
E. M., fixed	+1.36	-0.81	2.17	40.32	58.31	75.95	2nd	-3.55	
E. M., oscillating	+0.61	-0.36	0.97	17.43	27.79	33.95	2nd	-2.26	
C. O., fixed	+1.54	+0.86	0.68	10.29	16.66	23.80	3rd	-0.91	
C. O., oscillating	+1.66	+0.95	0.71	8.05	15.61	24.85	3rd	-1.08	
S. W., fixed	+0.60	-0.82	1.42	20.72	38.43	49.70	2nd	-2.78	
S. W., oscillating	+1.55	+0.68	0.87	11.90	16.24	30.45	2nd	-1.69	

II. RECOVERY						
Subject	Average Daily Balance through First 4 Weeks Gm.	Average Daily Gain through First 4 Weeks Gm.	Total N Retention, First 3 Weeks Gm.	Total N Retention, First 4 Weeks Gm.	Total N Retention, First 5 Weeks Gm.	Total N Retention, 6 Weeks Gm.
E. M., fixed	+2.15	0.79	8.54	22.12		
E. M., oscillating	+2.41	1.80	37.03	50.40	66.22	
C. O., fixed	+2.18†	0.64†	13.44			
C. O., oscillating	+1.97†	0.31†	6.44	14.28	22.89	
S. W., fixed	+2.21	1.61	24.22	45.01	61.53	73.29
S. W., oscillating	+2.49	0.94	21.63	26.46	30.38	34.79

* Control base-line balance in fixed bed experiment = average of last four control weeks; control base-line balance in oscillating bed experiment = average of last three control weeks.
† Data given for first three weeks, since in this subject in the fixed bed experiment balance studies were carried out only through the first three recovery weeks.

promptly began to retain nitrogen. By the end of the third week of recovery E. M. had regained all of the nitrogen lost during immobilization and thereafter stored additional nitrogen. C. O. and S. W. regained nearly all of their lost nitrogen by the end of the fifth recovery week. Maximum reten-

tion and oscillating bed experiments is presented in Figure 3 and Tables II and III.
2. Calcium: During the control periods the subjects were approximately in calcium equilibrium. During immobilization there was a gradual increase in calcium excretion. This increase occurred principally in the

urine, the increase in fecal calcium being small and variable. Urinary calcium excretion increased less rapidly than in the fixed bed experiment, and by the third to fourth week reached a plateau-like peak which was substantially lower than the

base-line excretion of each of the subjects was somewhat higher in the oscillating bed experiment, the rise in urinary calcium from the base-line and the total losses of calcium in the urine were considerably smaller during the immobilization in the

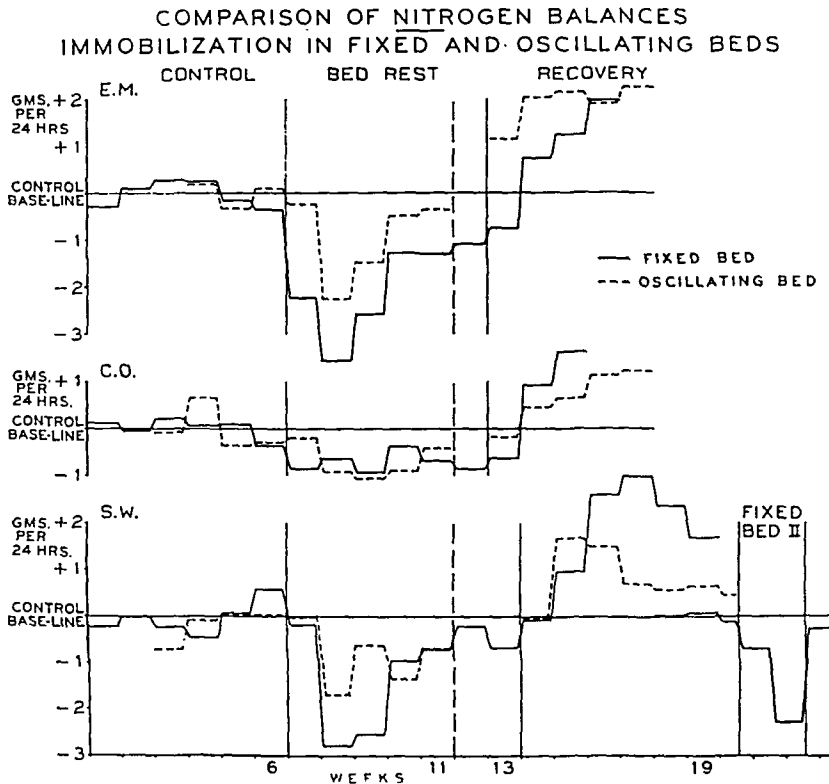


FIG. 3. Comparison of the changes in nitrogen metabolism resulting from immobilization in fixed and oscillating beds in three normal male subjects. The balances are plotted as deviations from the control baseline which in the fixed bed experiment was an average of the balances of the last four control weeks and in the oscillating bed experiment an average of the last three control weeks. In this and in each of the subsequent graphs "bed rest" indicates the immobilization phase of the experiments. The interrupted vertical line in the bed rest area of the graph marks the end of the five weeks during which the subjects were immobilized in oscillating beds; this convention has been adopted in each of the graphs in order to permit comparison of the metabolic and physiologic changes during an equal period of immobilization. "Fixed Bed II" refers to a two-week period of re-immobilization of subject S. W. in a fixed bed following recovery from immobilization in an oscillating bed.

levels reached during immobilization in the fixed bed. For all three subjects the maximal urinary calcium excretion (for a three- or four-day pooled specimen) ranged from 155 to 458 mg. per day with an average maximum of 311 mg. as contrasted with the maximum urinary calcium excretion of the same three subjects in the fixed bed, of 140 to 594 mg., with an average maximum of 362 mg. Since the control

oscillating bed. (Table IV and Fig. 4.) The average maximum increase in urinary calcium in the oscillating bed experiment was 121 mg., in the fixed bed experiment 233 mg. The total losses of calcium in the *urine* during immobilization in the oscillating bed averaged only 51 per cent of the total losses for the same period of time during immobilization in the fixed bed. The total losses (urinary plus fecal) in the oscillating bed

experiment averaged 46 per cent of the total losses in the fixed bed experiment. (Table v and Fig. 5.)

Factors influencing urinary calcium solubility showed little or no change. Urine volumes increased slightly (average daily

urine volumes averaged 250 cc. higher during the immobilization periods than during the control periods). Urinary pH rose between 0.1 and 0.2 units (the slight shift toward alkalinity being less favorable for calcium solubility). Citric acid excretion did not change significantly. These findings were the same as were observed in the fixed bed experiment.

During the recovery phase following immobilization in the oscillating bed calcium excretion receded toward control levels more rapidly than it did in the fixed bed experiment. In two of the subjects, C. O. and S. W., retention began at the second to third week and gradually became more marked throughout the five to six weeks during which recovery was studied. In E. M. calcium excretion approximately reached control levels at the third week but no appreciable calcium retention occurred.

The re-immobilization of subject S. W. for two weeks in a fixed bed resulted in a rise in urinary calcium at approximately the same rate as during his first immobilization in the fixed bed. The control base-line for this second fixed bed experiment was not at a closely comparable level to the control base-lines of the previous experiments

TABLE III
COMPARISON OF NITROGEN METABOLISM DURING A TWO WEEKS RE-IMMOBILIZATION IN FIXED BED WITH FIRST TWO WEEKS OF IMMOBILIZATION IN PREVIOUS FIXED AND OSCILLATING BED EXPERIMENTS

Experiment (Subject S. W.)	Control Base-line Balance Gm./ day	Devia- tion of N Balance during 2nd Week from Control Base- line Gm./day (for the week)	Increase above Control Level of Average Daily Urinary N Out- put during 2nd Week Gm./ day	Total N Loss during 2 Weeks Immo- biliza- tion Gm.
Fixed bed I.	+0.60	-2.78	2.77	20.72
Oscillating bed. . .	+1.55	-1.69	1.76	11.90
Fixed bed II.	+2.11*	-2.27	2.05	20.72

* Control base-line balance of second fixed bed experiment = average of last three periods (18 days) of oscillating bed experiment recovery phase.

TABLE IV
COMPARISON OF URINARY CALCIUM EXCRETION DURING FIVE WEEKS IMMOBILIZATION IN FIXED AND OSCILLATING BEDS

Subject	Control	Five-week Period of Immobilization					
	Control Base-line Urinary Calcium Output* Gm./day	Average Daily Urinary Calcium Output Gm.	Increase above Control Base-line of Average Daily Urinary Calcium Output Gm.	Total Urinary Calcium Loss Gm.	Maximum Urinary Calcium		
					Week of Occurrence	Maximum (for that week) Gm./day	Deviation from Control Base-line Gm./day
E. M., fixed.	0.050	0.100	0.050	1.75	4th	0.119	0.069
E. M., oscillating	0.096	0.130	0.034	1.19	5th	0.149	0.053
C. O., fixed.	0.116	0.274	0.158	5.53	5th	0.319	0.203
C. O., oscillating	0.223	0.284	0.061	2.13	3rd	0.306	0.083
S. W., fixed.	0.213	0.494	0.281	9.84	5th	0.577	0.364
S. W., oscillating	0.252	0.382	0.130	4.55	5th	0.445	0.193

* Control base-line urinary calcium output in fixed bed experiment = average of last four control weeks; control base-line urinary calcium output in oscillating bed experiment = average of last three control weeks.

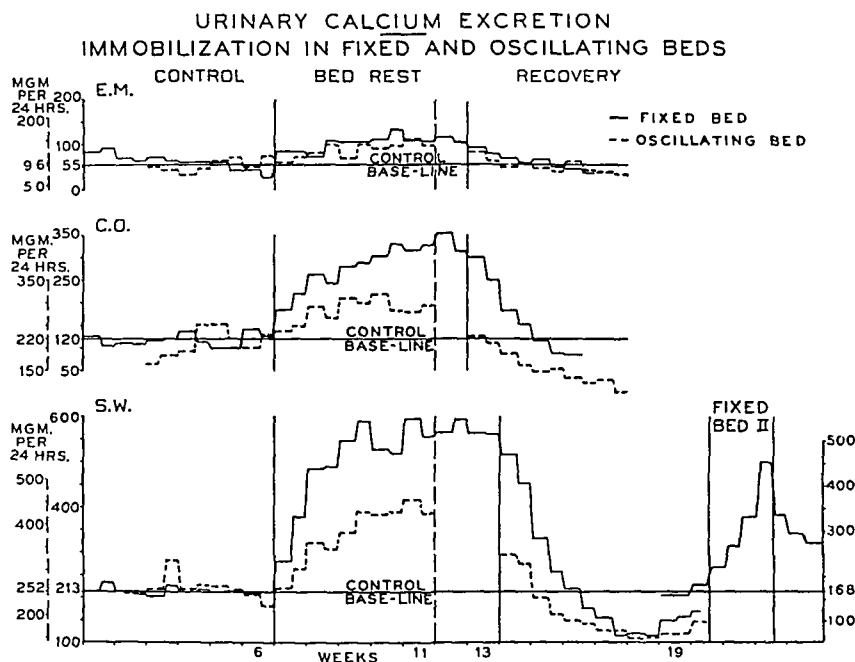


FIG. 4. Comparison of the changes in the urinary excretion of calcium resulting from immobilization in fixed and oscillating beds in three normal male subjects. The ordinate scales for urinary calcium excretion (in mg. per twenty-four hours) have been placed so that the control baselines of the fixed and oscillating bed experiments are superimposed. The control baseline urinary calcium excretion for the fixed bed experiment was an average of the outputs of the last four control weeks, for the oscillating bed experiment an average of the outputs of the last three control weeks; for the re-immobilization of subject S. W. in a fixed bed (Fixed Bed II) the control baseline was an average of the last two periods (eleven days) of the oscillating bed experiment recovery phase.

TABLE V
COMPARISON OF TOTAL CALCIUM METABOLISM DURING FIVE WEEKS' IMMOBILIZATION
IN FIXED AND OSCILLATING BEDS

Subject	Control	Five-week Period of Immobilization					Recovery Period		Total Calcium Deficit (A + B) Gm.
	Average Daily Balance* Gm.	Average Daily Balance Gm.	Average Daily Loss Gm.	Total Ca Loss during Immo- bilization (A) Gm.	Maximum Deviation from Control Base-line		No. of Weeks of Addi- tional Calcium Loss	Total Addi- tional Calcium Loss during Recovery (B) Gm.	
					Week of Occur- ence	Deviation Gm./day (for that week)			
E. M., fixed.....	+0.131	-0.026	0.157	5.50	5th	-0.280	4	2.76	8.26
E. M., oscillating	+0.055	-0.024	0.079	2.76	5th	-0.175	2	1.37	4.13
C. O., fixed.....	+0.130	-0.108	0.238	8.33	5th	-0.329	3	2.04	10.37
C. O., oscillating	+0.010	-0.058	0.068	2.38	5th	-0.157	1	0.99	3.37
S. W., fixed.....	+0.081	-0.253	0.334	11.69	5th	-0.500	3	5.25	16.94
S. W., oscillating	+0.101	-0.098	0.199	6.96	4th	-0.278	2	1.39	8.35

* Control base-line balance in fixed bed experiment = average of last four control weeks; control base-line balance in oscillating bed experiment = average of last three control weeks.

because some calcium retention was still going on six and one-half weeks following the immobilization in the oscillating bed. However, the prompt and marked increase in urinary calcium when S. W. was again placed in a fixed bed is evident. (Fig. 4.)

phorus began to increase promptly during immobilization and reached a peak at the second week, coinciding closely with the peak of urinary nitrogen excretion. A second peak of phosphorus excretion occurred at the fourth to fifth weeks at the time when

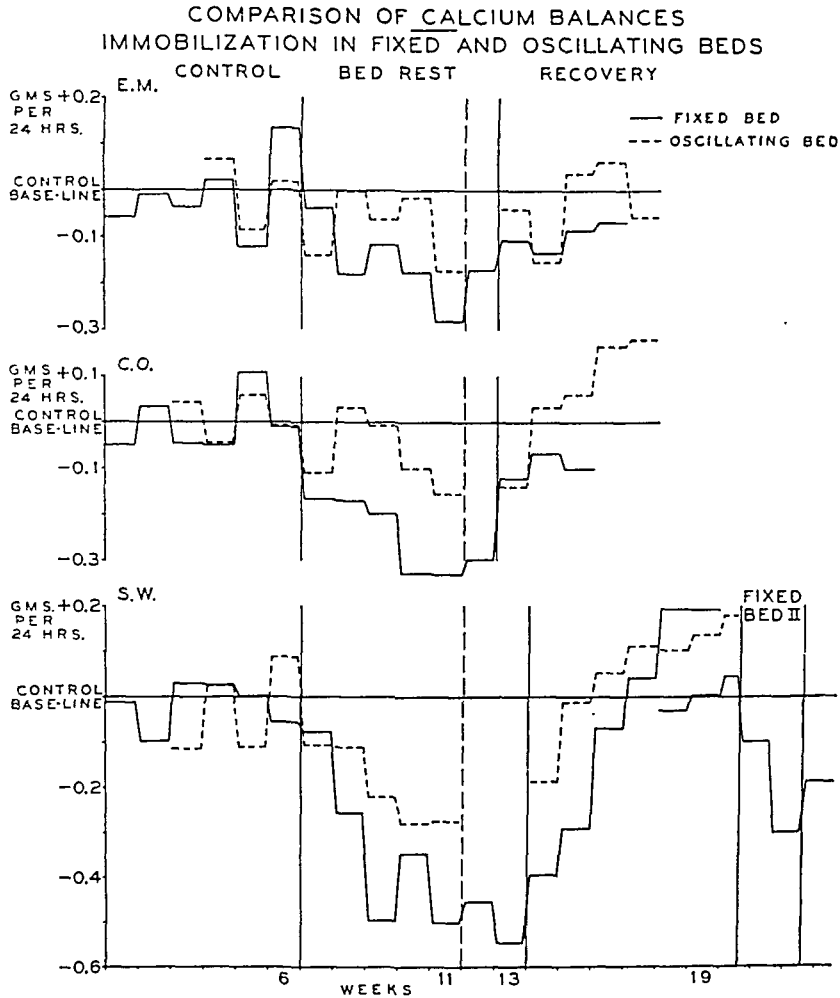


FIG. 5. Comparison of the changes in calcium metabolism resulting from immobilization in fixed and oscillating beds in three normal male subjects. The balances are plotted as deviations from the control baseline which in the fixed bed experiment was an average of the balances of the last four control weeks and in the oscillating bed experiment an average of the last three control weeks.

This increase was twice as great as occurred during the same length of time in the oscillating bed. (Table vi.)

3. *Phosphorus*: During the control phase the subjects maintained small positive balances as related to intake. During immobilization there was an increase in both urinary and fecal phosphorus excretion; the increase in fecal phosphorus, however, was very small and variable. Urinary phos-

phorus excretion was at maximum levels. During recovery phosphorus excretion fell rapidly to levels below the control base-line, greatest retention of phosphorus occurring at the third to fourth recovery weeks.

The total amounts of phosphorus lost during the five weeks' immobilization in the oscillating bed were significantly less than resulted in the fixed bed in two of the three subjects. (Table vii.) In E. M. and C. O.

TABLE VI

COMPARISON OF URINARY AND TOTAL CALCIUM METABOLISM DURING TWO WEEKS' RE-IMMOBILIZATION IN FIXED BED WITH FIRST TWO WEEKS OF IMMOBILIZATION IN PREVIOUS FIXED AND OSCILLATING BED EXPERIMENTS

Experiment (Subject S. W.)	Control		Two-week Period of Immobilization					
	Control Base-line Urinary Calcium Output Gm./day	Control Base-line Balance Gm./day	Average Daily Urinary Calcium Output during 2nd Week Gm./day	Maximum Urinary Calcium		Total Urinary Calcium Loss Gm.	Deviation of Ca Balance of 2nd Week from Control Base-line Gm./day	Total Calcium Loss (Urinary plus Fecal) Gm.
				Maximum, Derived from a 3- or 4-day Pooled Urine Specimen (during 2nd week) Gm./day	Deviation from Control Base-line Gm./day			
Fixed bed I.	0.213	+0.081	0.486	0.488	0.275	2.674	-0.255	2.317
Oscillating bed.	0.252	+0.101	0.355	0.361	0.109	0.910	-0.111	1.526
Fixed bed II.	0.168*	+0.235**	0.383	0.452	0.284	2.009	-0.300	2.786

* Control base-line urinary calcium output of second fixed bed experiment = average of last two periods (11 days) of oscillating bed experiment recovery phase.

** Control base-line balance of second fixed bed experiment = average of last three periods (18 days) of oscillating bed experiment recovery phase.

TABLE VII

COMPARISON OF PHOSPHORUS METABOLISM DURING FIVE WEEKS' IMMOBILIZATION IN FIXED AND OSCILLATING BEDS

Subject	Control	Five-week Period of Immobilization					
	Average Daily Balance * Gm.	Average Daily Balance Gm.	Average Daily Loss Gm.	Total Urinary Phosphorus Loss Gm.	Total Phosphorus Loss (Urinary Plus Fecal) Gm.	Maximum Deviation from Control Base-line	
						Week of Occurrence	Deviation Gm./day (for the week)
E. M., fixed.....	+0.328	+0.050	0.278	4.62	9.73	2nd	-0.373
E. M., oscillating ...	+0.151	+0.014	0.137	3.22	4.79	5th	-0.319
C. O., fixed.....	+0.278	+0.147	0.131	3.89	4.58	1st	-0.235
C. O., oscillating ...	+0.191	+0.105	0.086	2.38	3.01	4th	-0.188
						1st	-0.142
						4th	-0.103
S. W., fixed.....	+0.169	-0.046	0.215	7.49	7.53	3rd	-0.370
S. W., oscillating ...	+0.189	-0.046	0.235	7.70	8.22	2nd	-0.256
						4th	-0.288

* Control base-line balance in fixed bed experiment = average of last four control weeks; control base-line balance of oscillating bed experiment = average of last three control weeks.

the losses of phosphorus in the *urine* during immobilization in the oscillating bed were 70 per cent and 61 per cent, respectively, of the amounts lost by these two subjects in the urine during immobilization in the fixed bed; the total losses (urinary plus

in the fixed bed and during the first two weeks of immobilization in the oscillating bed and first fixed bed experiments were also nearly identical in this subject.

4. *Total sulfur*: The ratio of urinary total sulfur to urinary total nitrogen during the

TABLE VIII
RATIO OF URINARY NITROGEN TO URINARY TOTAL SULFUR
(OSCILLATING BED EXPERIMENT)

Periods	Subject E. M.			Subject C. O.			Subject S. W.		
	Average Daily Urinary Nitrogen Gm.	Average Daily Urinary Total Sulfur Gm.	N:S Ratio	Average Daily Urinary Nitrogen Gm.	Average Daily Urinary Total Sulfur Gm.	N:S Ratio	Average Daily Urinary Nitrogen Gm.	Average Daily Urinary Total Sulfur Gm.	N:S Ratio
Control									
Last four weeks	14.09 12.67 12.95 12.72	0.912 0.823 0.826 0.842	15.44 15.39 15.68 15.13	11.30 10.48 11.93 11.73	0.683 0.645 0.759 0.759	16.55 16.24 15.73 15.48	11.94 11.86 11.29 11.66	0.783 0.745 0.755 0.790	15.26 15.92 14.96 14.78
Average of last 3 control weeks.	12.78	0.830	15.40	11.38	0.721	15.80	11.61	0.763	15.22
Immobilization									
1st week.	12.57	0.797	15.78	11.64	0.740	15.74	11.56	0.770	15.03
2nd week.	14.81	0.888	16.69	12.69	0.762	16.65	13.36	0.875	15.27
3rd week.	14.27	0.884	16.13	12.85	0.778	16.52	12.55	0.848	14.80
4th week.	13.34	0.883	15.12	12.34	0.775	15.93	13.15	0.840	15.66
5th week.	13.04	0.845	15.44	11.70	0.757	15.48	12.51	0.835	14.99
Recovery									
1st week.	11.77	0.765	15.39	11.35	0.705	16.10	11.93	0.788	15.14
2nd week.	10.70	0.686	15.60	10.60	0.686	15.47	10.12	0.700	14.48
3rd week.	10.79	0.733	14.73	10.37	0.693	14.97	10.37	0.680	15.26
4th week.	10.92	0.735	14.88	10.03	0.688	14.60	11.29	0.753	15.00
5th week.	10.06	0.692	14.56	9.91	0.680	14.60	11.36	0.755	15.06
6th week.							11.30	0.773	14.62

fecal) were 49 per cent and 65 per cent, respectively, of the total amounts lost during immobilization in the fixed bed. In S. W. the total phosphorus loss (urinary plus fecal) during the five weeks' immobilization in the oscillating bed exceeded the total loss during five weeks in the fixed bed by 9 per cent. The amounts lost in the *urine* by this subject were nearly identical for five weeks' immobilization in both experiments; the amounts of phosphorus lost in the urine during the two weeks of re-immobilization

last three control weeks was 1:15.4 for E. M., 1:15.8 for C. O. and 1:15.2 for S. W. As in the fixed bed experiment, this sulfur:nitrogen ratio was maintained quite constantly from week to week throughout the immobilization and recovery period, suggesting a sulfur rich source for the excreted nitrogen, presumably muscle in large measure. (Table VIII.)

5. *Potassium*: During the control phase the subjects were approximately in potassium equilibrium. During the first week or

first two weeks of immobilization potassium excretion increased in all three subjects. Thereafter there was wide variation among the subjects. In E. M. the excretion of potassium remained elevated throughout the immobilization period declining toward equilibrium during the last two weeks; his total loss of potassium was 7.63 Gm. In S. W. potassium was lost during the first three weeks of immobilization and retained during the last two weeks, yielding a net loss of 1.75 Gm. C. O. exhibited a marked potassium retention during the last three weeks of immobilization so that his overall balance for the five weeks was +6.3 Gm. In spite of these marked individual variations in potassium excretion, the balances of all three subjects were less negative during immobilization in the oscillating bed than during the same length of time in the fixed bed.

6. *Sodium*: During immobilization sodium excretion increased slightly. The increase occurred only in urinary excretion, fecal excretion remaining less than 0.04 Gm. daily during all phases of the experiment. The total losses of sodium ranged from 3.85 Gm. to 8.75 Gm. during five weeks' immobilization.

During recovery sodium excretion diminished to control levels. In two subjects sodium retention did not occur. In the third subject retention occurred only during the first two recovery weeks.

Sodium balance studies had been carried out in both the fixed and oscillating bed experiments in only one subject, S. W. In this subject the total sodium loss was 6.72 Gm. during five weeks in the fixed bed, 8.75 Gm. during five weeks in the oscillating bed.

7. *Creatine metabolism*: As in the fixed bed experiment, urinary creatinine excretion remained quite constant throughout all periods of study. Creatine excretion showed day to day fluctuations at a low level (dietary intake not creatine-free), but no significant shifts occurred from one phase of study to the next. However, the decreases in creatine tolerance occurring as a result

of immobilization were significantly altered by the use of the oscillating bed. Although creatine tolerance also declined progressively during the immobilization stage of this experiment, the extent of decline was considerably less than during immobilization

TABLE IX
COMPARISON OF CREATINE TOLERANCE TESTS (PER CENT RETENTION OF FED CREATINE) IN FIXED BED AND OSCILLATING BED EXPERIMENTS

Periods	Subject E. M.		Subject C. O.		Subject S. W.	
	Fixed Bed	Oscillating Bed	Fixed Bed	Oscillating Bed	Fixed Bed	Oscillating Bed
Control last six weeks	88	91	...
	100	...	98	84
	99	98	91	99	89	...
	...	97	...	100	...	100
	...	100	98	100	80	100
Immobilization						
1st week....	83	82
2nd week....	...	87	29	93	46	...
3rd week....	56	...	26	64
4th week....	76	88	50	81	48	73
5th week....	...	81	24	42	44	73
6th week....	70	13	...
Recovery						
1st week....	70	...	27
2nd week....	...	98	...	73	73	84
3rd week....	91	100	90	100	...	99
4th week....	100	...	95	...	100	...
5th week....	...	100	...	95	98	89
6th week....	100	93

in the fixed bed experiment. (Table ix.) The lowest percentages of creatine retention in tests of creatine tolerance during immobilization in the oscillating bed were 81 per cent, 42 per cent and 64 per cent for E. M., C. O. and S. W., respectively. During the same period of immobilization in the fixed bed the lowest percentages of retention were in the same order 70 per cent, 24 per cent and 13 per cent.

8. *17-Ketosteroids*: The excretion of 17-ketosteroids over the entire period of immobilization gave average values which were not significantly lower than those for the control and recovery periods. There was in all three subjects a slight and questionably significant reduction toward the end of the immobilization period. The absence of any correlation between the

changes in nitrogen excretion and 17-ketosteroid excretion is evident in Table x.

In the previous immobilization study only one subject, E. M., had shown a significant decrease in 17-ketosteroid excre-

TABLE X
URINARY 17-KETOSTEROID EXCRETION (ANALYSES OF SEVEN-DAY POOLED URINE SPECIMENS) AND COMPARISON WITH TOTAL NITROGEN EXCRETION—OSCILLATING BED EXPERIMENT

Periods	Subject E. M.		Subject C. O.		Subject S. W.	
	17-keto-steroids Mg./ day	Nitro- gen Total Excretion Gm./ day	17-keto-steroids Mg./ day	Nitro- gen Total Excretion Gm./ day	17-keto-steroids Mg./ day	Nitro- gen Total Excretion Gm./ day
Control						
1st week.....						13.43
2nd week....	11.05	15.38	12.85	12.86	11.50	13.59
3rd week.....	8.82	13.61	11.05	11.98	12.10	12.97
4th week.....	9.30	14.17	9.35	13.15	13.05	12.81
5th week.....	8.93	13.74	11.80	13.12	11.70	12.85
Average of last 3 control weeks.	9.02	13.84	10.73	12.75	12.28	12.88
Immobilization						
1st week.....	10.50	14.07	11.62	13.00	14.20	12.89
2nd week.....	9.22	16.10	11.50	13.73	13.50	14.62
3rd week....	8.90	15.32	11.10	13.87	10.80	13.77
4th week.....	8.30	14.34	9.85	13.69	10.01	14.51
5th week.....	7.90	14.20	9.18	13.20	10.64	13.85
Average of immobilization weeks.....	8.96	14.81	10.65	13.50	11.83	13.93
Recovery						
1st week.....	7.12	12.70	10.75	12.98	11.85	13.27
2nd week.....	10.55	11.83	10.50	12.33	10.70	11.48
3rd week....	8.10	11.70	11.60	12.14	9.45	11.66
4th week.....	9.95	11.92	11.05	11.67	8.85	12.51
5th week.....	9.25	11.59	12.72	11.56	7.48	12.59
6th week.....					8.55	12.54
Average of recovery weeks	8.99	11.95	11.32	12.14	9.48	12.34

tion during the period of immobilization in the fixed bed.

9. Other factors in the urine: Urinary specific gravity measured daily did not change significantly during the various periods of study. On fairly constant fluid intake levels, averaging approximately 2,300 cc. daily, the average daily urine volumes among the three subjects were approximately 250 cc. higher during immobilization than during the control phase. An increase in urine volume of the same extent occurred during

the immobilization period in the fixed bed experiment.

10. Blood chemistry studies: There were no significant changes in the blood levels of total proteins, phosphorus, sodium and potassium during immobilization in the oscillating bed.

During immobilization in the fixed bed elevations in serum calcium levels were observed in all four subjects. In the present experiment changes in serum calcium were less striking. (Table xi.) In two of the subjects (E. M. and S. W.) the average serum calcium levels during immobilization were slightly higher than the average levels during the control phase.

B. Physiologic Studies. 1. Basal metabolism. Tests of the basal metabolic rate showed a decline among all three subjects during immobilization which ranged from 0.9 to 1.4 calories per square meter per hour. This represents a bare 3.4 per cent average reduction in basal oxygen consumption during immobilization in the oscillating bed. In the fixed bed experiment for these three subjects a 5.1 per cent reduction was found in basal metabolism during immobilization. In the recovery phase following immobilization in the oscillating bed, basal metabolism returned to control levels in two to three weeks.

Determinations on two subjects while the bed was cscillating did not show a significant difference between oxygen consumption during oscillation and in the stationary horizontal position. Oscillation at the speed employed appeared not to increase oxygen consumption in the basal state in the limited number of determinations carried out.

2. Muscle strength: Comparison of the decreases in muscle strength during five weeks' immobilization in the fixed and oscillating bed experiments revealed that in the oscillating bed there was a smaller reduction in muscle strength particularly in the immobilized leg muscles.

Strength of the biceps muscle groups showed an average decline among the three subjects of a little less than 5 per cent in each experiment. Strength of the shoulder

and arm muscles tested by the straight arm pull showed an average decline of 8.2 per cent during five weeks in the fixed bed and 3.4 per cent in the oscillating bed. In the leg muscles the strength of the anterior tibial muscle groups declined on an average

3. *Girth of extremities:* Girth of the thighs and calves decreased during the five weeks' immobilization in the oscillating bed to a slightly smaller extent than they had decreased during the same length of time in the fixed bed.

TABLE XI
CHANGES IN SERUM CALCIUM LEVELS DURING IMMOBILIZATION IN OSCILLATING BED

Subject	Control		Five Weeks' Immobilization			Recovery	
	No. of Determinations	Range and Average Value Mg./100 cc.	No. of Determinations	Range and Average Value Mg./100 cc.	Week of Occurrence of Maximal Value	No. of Determinations	Range and Average Value Mg./100 cc.
E. M.	3	11.2 (10.6-11.8)	2	12.4 (12.2-12.6)	3rd	2	11.6 (11.5-11.8)
C. O.	3	12.3 (11.9-13.0)	2	12.2 (11.8-12.7)	5th	2	11.5 (11.5-11.6)
S. W.	3	10.7 (10.5-11.1)	5	11.1 (9.4-12.3)	3rd	2	10.7 (10.3-11.1)

14.3 per cent in the fixed bed and 9.2 per cent in the oscillating bed. The decline in strength of the gastrocnemius-soleus muscle groups in the fixed bed ranged from 13.2 per cent to 26.6 per cent with an average decline of 20.2 per cent; in the oscillating bed the decline in strength ranged from 10.9 per cent to 23.8 per cent with an average decline of 15.6 per cent.

In the recovery phase of the oscillating bed experiment approximately three weeks were required for muscle strength to return to control levels. The time required for recovery of muscle strength was slightly longer (approximately four weeks) following immobilization in the fixed bed.

The re-immobilization of S. W. in a fixed bed for two weeks resulted in a decline of 10 per cent on the average in the strength of the anterior tibial and gastrocnemius-soleus muscle groups. During the first two weeks of immobilization in the first fixed bed experiment the average decline in strength of these muscle groups was 11 per cent, but during the same period of time in the oscillating bed the decline in strength was only 2 per cent.

Analysis of the decreases in the girth of the *thighs* in the two experiments revealed differences which, though not statistically significant, were all in the direction of smaller decreases in girth in the oscillating bed. Analysis of the *calf* measurements of subject S. W., all of which were made with the accurate device previously described,¹ revealed significantly smaller decreases in the oscillating bed experiment. The girth of the calves in S. W. decreased by 4.2 per cent in the oscillating bed and by 5.7 per cent during five weeks in the fixed bed. In subjects E. M. and C. O. measurements made during the fixed bed experiment were not strictly reliable since they were made with a narrow steel tape. However, in each leg of both subjects the decreases in girth of the calves were consistently smaller in the oscillating bed experiment although in subject C. O. the differences were very slight.

Comparison of the girth measurements of S. W. during the two weeks' re-immobilization in the fixed bed with the first two weeks of immobilization in the previous fixed and oscillating bed experiments showed approxi-

mately equal decreases in thigh and calf circumferences in all three experiments.

4. *Tilt table:* Use of the oscillating bed during immobilization tended to prevent deterioration of the mechanisms essential for circulatory control in the erect position,

was reached at which circulation became impaired, dizziness and pallor appeared and fainting followed shortly thereafter.

Figure 6 presents a comparison of the results of tilt table tests in the fixed and oscillating bed experiments, showing the

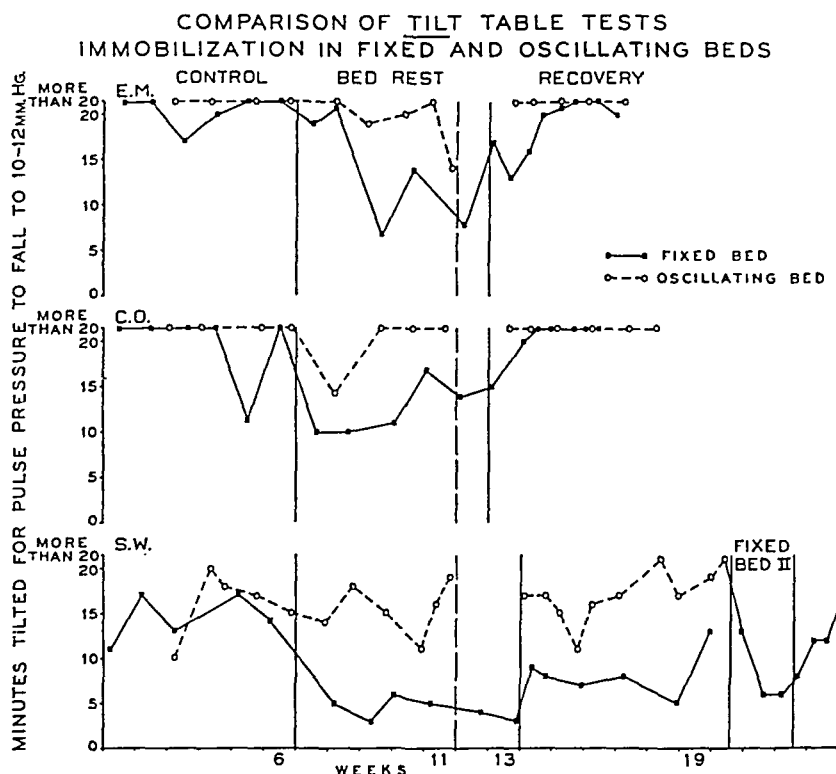


FIG. 6. Comparison of the effect of immobilization in fixed and oscillating beds on the results of tilt table tests, showing the number of minutes in the tilted position (65 degrees feet downward) required for the pulse pressure to fall to critical levels of 10 to 12 mm. of Hg.

which had been found to occur during immobilization of the same subjects in fixed beds. This effect of the oscillating bed was indicated by the uniformly improved reaction of the subjects' circulation and decreased tendency to faint in tilt table tests.

Analysis of tilt table tests performed during the fixed bed experiment and correlation of the data on pulse rate and blood pressure with the observed general reactions of the subjects indicated that the pulse pressure was the most important factor involved in the response of the circulation to tilting. With the subject standing in the upright position on the tilt table it was found that when the pulse pressure fell to between 10 and 12 mm. of mercury, a critical level

number of minutes required for the pulse pressure to fall to the critical levels of 10 to 12 mm. when the subjects were tilted to 65 degrees, feet downward. In the fixed bed experiment, during the immobilization phase some impairment of circulatory control began to take place within one week, and the number of minutes required to reach critical pulse pressure levels became markedly reduced within two to three weeks so that actual fainting frequently occurred. In the oscillating bed experiment during the immobilization phase circulatory control was maintained almost at the control level. In the recovery period circulatory control on the tilt table fully returned to the control level within two weeks in this

experiment whereas three to four weeks were required in the fixed bed experiment.

The re-immobilization of S. W. in a fixed bed for two weeks brought about essentially the same degree of circulatory deterioration as had occurred during immobilization in the first fixed bed experiment, only six to eight minutes being required for critical pulse pressure levels to be reached.

Tiny purpuric hemorrhages in the skin of the feet and legs had occurred in all three subjects in tilt table tests during the latter part of the immobilization phase in the fixed bed experiment. However, in the oscillating bed experiment no petechial hemorrhages appeared in any subject.

5. *Blood volume:* The fall in plasma volume and total blood volume during immobilization was almost identical in the fixed and oscillating bed experiments. The decreases in blood volume averaged slightly less during the immobilization in the oscillating bed but not significantly so.

In the fixed bed experiment during immobilization the average decrease in plasma volume in the three subjects was 217 cc. or 6.9 per cent, in total blood volume 295 cc. or 5.7 per cent. In the oscillating bed the average decrease in plasma volume was 190 cc. or 5.9 per cent, in total blood volume 234 cc. or 4.3 per cent.

Re-immobilization of S. W. for two weeks in a fixed bed brought about a 5.0 per cent decrease in plasma volume and 5.2 per cent decrease in total blood volume.

6. *Circulation time:* Decholin and macasol circulation times showed no changes during immobilization in either the fixed or oscillating bed experiments.

7. *Blood coagulation studies:* Studies employed on all three subjects were coagulation time as determined by the Lee-White method and prothrombin time by a modification of the method of Herbert. Coagulation times following the injection of 1 cc. of heparin intravenously both by the Lee-White and capillary tube methods were carried out at approximately two-week intervals on subject S. W., and prothrombin

time determinations by the Link-Shapiro method were carried out every other day during the week preceding and the two weeks of re-immobilization of S. W. in a fixed bed. None of these studies indicated a significant influence of bed rest upon blood coagulation.

8. *Exercise tolerance tests:* As in the fixed bed experiment Master tests showed a decrease in exercise tolerance following immobilization. The recovery of exercise tolerance to control levels required three to four weeks following the immobilization in the oscillating bed as against four to six weeks following the immobilization in the fixed bed.

9. *Heart size:* Kymograms of the chest failed to reveal any significant changes in heart size during this experiment. With this technic, as with the standard chest x-ray technic employed in the fixed bed experiment, there was considerable variation in the apparent size of the heart.

10. *Electrocardiograms:* Electrocardiograms taken in the resting horizontal position during control and immobilization periods showed that during immobilization the heart rate was slightly increased and T₂ decreased in height between 1 and 3 mm. These changes were similar to those which occurred during immobilization in the fixed bed.

11. *Resting pulse rate and blood pressure:* During immobilization in the oscillating bed the resting pulse rate increased on an average 3.0 beats per minute (4.3 beats per minute in the fixed bed). During the first three weeks of recovery there was an additional average increase of 3.1 beats per minute, (3.7 beats in the fixed bed). After the third recovery week in both experiments the resting pulse rate declined toward the control level. In the oscillating bed experiment the control level was reached at approximately the fifth recovery week; in the fixed bed experiment the resting pulse rates had not quite reached the control level by the end of the sixth week.

Resting arterial systolic and diastolic

blood pressures did not change significantly in either experiment.

12. *Hematocrits and blood counts:* No significant changes attributable to immobilization occurred in hematocrits, blood cell counts or hemoglobin estimations. There

TABLE XII
CHANGES IN BODY WEIGHT DURING THE OSCILLATING BED
EXPERIMENT

Subject	Control	Immobilization		Recovery	
	Weight Change (Last Three Weeks) Kg.	No. of Weeks	Weight Change Kg.	No. of Weeks	Weight Change Kg.
E. M.	-0.4	5	-0.7	5	+1.2
C. O.	+0.4	5	+1.1	5	-0.2
S. W.	-0.8	5	-1.2	6	-0.7

was a gradual fall in hematocrits throughout the experiment ranging from 2.3 to 3.3 volumes per cent, which may be partially accounted for by the withdrawal of blood for chemical studies.

13. *Body weight:* As in the fixed bed experiment changes in body weight were small during the various periods of study. (Table XII.)

14. *Various observations of circulation and respiration during oscillation:* An indication of the effect of oscillation upon the venous circulation of the legs and upon the venous return of blood to the heart may be obtained from the continuous direct measurements of venous pressure in the foot veins during oscillation. The average change in venous pressure in subject C. O.'s dorsal foot vein with each change in position of the bed was 136 mm. of water, and in subject S. W.'s dorsal foot vein 148 mm. of water. Observations of foot veins during oscillation revealed that the veins filled in the foot-down position and emptied in the horizontal. Measurements of foot vein to tongue or carotid circulation time were not made.'

There was a constant rhythmical varia-

tion in the pulse rate of the subjects during oscillation, the pulse rate being slowest in the horizontal position, speeding up gradually as the bed tilted, being the most rapid at the maximum foot-down position then decreasing gradually as the bed rocked back to the horizontal position. The pulse rate was approximately 10 to 12 beats per minute, more rapid in the foot-down position than in the horizontal position.

Tracings of the respiration of the subjects during oscillation made with a pneumograph and with a spirometer showed changes in the average level or position of the diaphragm with each change in position of the bed. As the bed tilted into the foot-down position, the diaphragm and rib cage shifted gradually into a definite inspiratory position; as the bed rocked back to the horizontal position, the diaphragm and rib cage shifted gradually back to the original mid-position. Despite these shifts in the position of the diaphragm, minute ventilation at rest was not greater during oscillation than in the stationary horizontal position.

PSYCHOBIOLOGIC EFFECTS OF IMMOBILIZATION
IN AN OSCILLATING BED*

The three subjects of this experiment, none of whom had a major psychiatric disorder, were studied to determine the psychobiologic effects of immobilization in an oscillating bed. Data were collected by psychiatric interviews and recorded on a check list of daily experiences. The list contained sixty-five items relating to physical and mental activity and energy, psychosomatic reactions, mood changes, sleep, sexual behavior and reactions to doctors, nurses and visitors.

The data revealed that the reactions to immobilization were markedly variable from subject to subject, both in pattern and degree, and were expressions of the subject's dominant personality traits.

A subject's immediate reaction to im-

* From the Department of Medicine (Neurology), Cornell University Medical College. This work was carried out by Dr. Keeve Brodman.

mobilization (such as dependency, aggression or suppression of all emotion) was similar to that experienced in other situations of stress and danger, each subject according to his own dominant personality traits. These reactions occurred most markedly during the two days early in the control period when the cast was fitted, again during the first forty-eight hours of immobilization and once more during the first few days after the cast had been removed. In the five weeks of immobilization each subject manifested, either overtly or indirectly, some signs of anxiety, hostility and increased sexual tension. Changes also took place in mental activity, physical activity and the sleep pattern. Complaints of physical discomfort such as impaired sleep and stiffness and soreness of the muscles were minimal and were rarely expressed after the first week. Stiffness of the knees occurred in one subject; this was slight and was present only during the final week in the cast.

Certain physiologic phenomena, such as decrease in appetite, generalized weakness and increased fatigue on exertion were clearly less marked than they had been in a previous immobilization in a fixed bed. In recovery mild dizziness was noted only momentarily, unsteadiness of the legs lasted to the third recovery day, and weakness of the legs for ten days. The subject who reported stiffness of the knees during the final week in the cast continued to have it to a slight degree for three weeks in recovery; this was the same subject who following immobilization in the fixed bed had noted knee stiffness and soreness for several months. The reduction in intensity of these physiologic phenomena is associated with both psychosomatic factors and the effects of oscillation on the circulation.

In all instances these reactions were markedly less than had been noted one year previously when each of the three subjects was immobilized in a fixed bed. Since these reactions are similar to those the subjects experienced in other situations of stress and danger and since in their first experience

the subjects had discovered that immobilization was not really to be feared, it would seem that the relative mildness of the reactions in the oscillating bed was related to the fact that this was a second experience with immobilization and not that the bed oscillated. This interpretation is borne out by observations on a subject (S. W.) who, after having been in a fixed bed and then in an oscillating bed, was immobilized for a third time in a fixed bed. In this third experience, with the exception of muscle stiffness, he had even milder reactions than in the oscillating bed.

COMMENTS

It would appear from these studies that motion of an oscillating bed of the Sanders type modifies favorably or prevents in large measure many of the metabolic and physiologic consequences of immobilization of the healthy adult. In Sanders' description of such a bed in 1936 its use was recommended as an adjuvant in the treatment of congestive heart failure and peripheral vascular disease,¹¹ and the bed since then has been used principally in the treatment of occlusive arterial disease of the extremities¹⁷⁻²⁰ and to some extent of phlebotrombosis and thrombophlebitis.^{21,22} The present study would suggest that the oscillating bed might also be of benefit in the management of patients who by the nature or severity of their illness are condemned to many weeks of relative immobility.

Influence of Oscillating Bed on Nitrogen Metabolism. Nitrogen losses from immobilization were reduced by approximately 50 per cent in two of the three subjects. There was an associated reduction in the loss of the muscle mass of the legs and in the extent of impairment of muscle strength and creatine metabolism as indicated by the creatine tolerance test. In the third subject (C. O.) the nitrogen loss was rather small in both the fixed and oscillating bed experiments. The oscillating bed was less effective in preventing impairment of muscle mass and strength, the decreases in both being approximately those experi-

enced during his previous immobilization in the fixed bed.

Correlation of Changes in Nitrogen Metabolism with Concomitant Changes in Sulfur, Phosphorus and Potassium. It has been of interest to determine whether the alterations in nitrogen metabolism observed in these studies could be correlated with changes in other protoplasmic constituents, such as sulfur, phosphorus and potassium. It is customary to calculate theoretic nitrogen balances based on the ratio of these elements to nitrogen in muscle protoplasm. Comparison with the measured nitrogen balances would indicate whether or not the reduced nitrogen loss brought about by oscillation represents a saving to the organism of muscle protoplasm. (Tables XIII to XV.)

Sulfur: The generally accepted sulfur:nitrogen ratio in muscle is 1:14. In this study in which only the total urinary sulfur was estimated, the ratio of urinary sulfur:nitrogen was maintained quite constantly throughout the study in the proportion in which these elements are present in muscle protoplasm. This was also the case in the previous study of immobilization in the fixed bed.

Phosphorus: The same calculation was made with respect to phosphorus, assuming a ratio of nitrogen:phosphorus in muscle of 14.7:1^{23,24,25} and correcting for phosphorus associated with calcium in the ratio in which these elements are present in bone (1:2.23^{24,26}). Although comparison of the theoretic nitrogen balances based on phosphorus excretion revealed a fair agreement from week to week with the measured nitrogen balances, there were significant discrepancies in the total excretion over the five-week period of immobilization. In all three subjects nitrogen excretion during immobilization in the oscillating bed was less by 34 per cent, 12 per cent and 60 per cent, respectively, than was anticipated from the phosphorus excretion. The average ratio of the nitrogen lost to phosphorus lost was 9.4:1 instead of the theoretic 14.7:1. This was in sharp contrast to the findings during five weeks' immobilization in the fixed bed.

In only one subject (E. M.) was the nitrogen excretion less (by 29 per cent) than was expected on the basis of phosphorus excretion; in the other three subjects the nitrogen excretion was significantly greater than that calculated from the phosphorus excretion. Thus, during the first five weeks' immobilization in the fixed bed for the same subjects employed in the oscillating bed experiment the average nitrogen:phosphorus loss showed a ratio of 20.3:1. There was no obvious explanation for the discrepancies between these nitrogen:phosphorus ratios and the theoretic ratio of 14.7:1.

These findings suggest the hazards of assuming such a fixed ratio of nitrogen:phosphorus in interpreting metabolic data. It should be pointed out that phosphorus appears to be deposited in protoplasm not only with nitrogen but also with carbohydrate, a circumstance that may in part be responsible for the discrepancies observed. In this connection attention is called to the absence of the expected correlation between the nitrogen and phosphorus changes and the changes in body weight.

Potassium: Analysis of potassium balances in relation to nitrogen excretion is also of interest in this connection because potassium, being the principal intracellular cation, may reflect the extent of protoplasmic catabolism and anabolism. The ratio of nitrogen:potassium in muscle is generally assumed to be 9.5:1 on the basis of surprisingly few chemical analyses in animals and man,^{25,28} considering the weight that has been given to this index in metabolic calculation. In both the fixed and oscillating bed experiments potassium tended to move in the same direction as nitrogen. Both elements were lost during the immobilization phase but the quantitative relationships were far from the theoretic. There were wide variations in potassium excretion from week to week, which were particularly marked in the oscillating bed experiment in which there were also pronounced variations from subject to subject. All three subjects sustained

TABLE XIII
METABOLIC BALANCES, SUBJECT E. M., SEVEN-DAY PERIODS
ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen					Calcium					Phosphorus					Potassium					Sodium									
	Output			Variation from Control	Balance	Output			Variation from Control	Balance	Output			Variation from Control	Balance	Output			Variation from Control	Balance	Output			Variation from Control	Balance					
	Intake	Feces	Urine			Intake	Feces	Urine			Intake	Feces	Urine			Intake	Feces	Urine			Intake	Feces	Urine			Intake	Feces	Urine	Intake	Feces
Control																														
i	14.41	14.09	1.29	15.38	-0.94	-1.55	0.918	0.880	0.903	0.991	-0.073	-0.128	1.023	1.010	0.680	1.690	-0.067	-0.218	3.763	5.20	4.77	3.99	-0.23	-0.33	4.00	3.90	0.014	3.91	+0.09	-0.14
ii	14.15	12.67	0.91	13.61	+0.81	+0.23	0.918	0.079	0.717	0.766	+0.122	+0.067	1.591	0.866	0.526	1.392	+0.199	+0.048	3.763	3.32	0.363	3.98	+0.08	-0.02	4.00	4.00	0.011	4.01	-0.01	-0.24
iii	11.45	12.95	1.23	14.17	+0.28	-0.33	0.919	0.107	0.843	0.950	-0.031	-0.086	1.591	0.894	0.629	1.523	+0.068	-0.083	3.763	2.70	0.477	3.75	+0.01	-0.09	4.00	3.65	0.013	3.66	+0.34	+0.11
iv	11.45	12.72	0.92	13.74	+0.71	+0.10	0.919	0.101	0.743	0.844	+0.075	+0.020	1.572	0.818	0.567	1.385	+0.187	+0.036	3.763	1.70	0.384	3.55	+0.21	+0.11	4.00	3.63	0.011	3.64	+0.36	+0.13
Control base-line																														
Average last three weeks	14.45	12.78	1.06	13.84	+0.61	0.0	0.919	0.096	0.768	0.864	+0.055	0.0	1.584	0.859	0.574	1.433	+0.151	0.0	3.763	2.50	0.408	3.66	+0.10	0.0	4.00	3.76	0.012	3.77	+0.23	0.0
Immobilization in oscillating bed																														
v	11.45	12.57	1.50	14.07	+0.38	-0.23	0.919	0.108	0.897	1.005	-0.086	-0.141	1.591	0.986	0.689	1.675	-0.084	-0.235	3.763	6.30	0.453	4.08	-0.32	-0.42	4.00	4.02	0.017	4.04	-0.04	-0.27
vi	11.45	14.81	1.29	16.10	-1.05	-2.26	0.919	0.133	0.733	0.866	+0.053	-0.002	1.591	1.043	0.500	1.633	-0.042	-0.193	3.763	6.00	0.360	3.96	-0.20	-0.30	4.00	3.78	0.013	3.79	+0.21	-0.02
vii	11.45	11.27	1.05	15.32	-0.87	-1.48	0.919	0.126	0.800	0.926	-0.007	-0.062	1.591	0.958	0.626	1.584	+0.007	-0.144	3.763	4.70	0.432	3.90	-0.14	-0.24	4.00	3.60	0.015	3.62	+0.38	+0.15
viii	11.45	13.34	1.00	11.31	+0.11	-0.50	0.919	0.137	0.743	0.880	+0.039	-0.016	1.591	0.901	0.582	1.483	+0.108	-0.043	3.763	2.90	0.392	3.68	+0.08	-0.02	4.00	4.05	0.012	4.06	-0.06	-0.29
ix	14.45	13.01	1.16	14.20	+0.25	-0.36	0.919	0.149	0.890	1.039	-0.120	-0.175	1.572	0.867	0.624	1.491	+0.081	-0.070	3.763	3.30	0.467	3.77	-0.01	-0.11	4.00	3.86	0.016	3.88	+0.12	-0.11
Average of immobilization	11.45	13.61	1.20	14.81	-0.36	-0.97	0.919	0.130	0.813	0.943	-0.024	-0.079	1.587	0.951	0.622	1.573	+0.014	-0.137	3.763	4.60	0.421	3.88	-0.12	-0.22	4.00	3.86	0.015	3.88	+0.12	-0.11
Recovery																														
x	11.45	11.77	0.93	12.70	+1.75	+1.14	0.918	0.117	0.786	0.903	+0.015	-0.040	1.609	0.830	0.582	1.412	+0.197	+0.046	3.763	2.70	0.326	3.60	+0.16	+0.06	4.00	3.55	0.012	3.56	+0.44	+0.21
xi	14.15	10.70	1.13	11.83	+2.62	+2.01	0.919	0.094	0.924	1.018	-0.099	-0.154	1.572	0.723	0.606	1.419	+0.153	+0.092	3.763	1.70	0.409	3.58	+0.18	+0.08	4.00	4.04	0.016	4.06	-0.06	-0.29
xii	11.15	10.70	0.91	11.70	+2.75	+2.14	0.918	0.085	0.740	0.825	+0.093	-0.038	1.591	0.780	0.574	1.354	+0.237	+0.086	3.763	1.50	0.350	3.50	+0.26	+0.16	4.00	3.84	0.012	3.85	+0.15	-0.08
xiii	14.15	10.92	1.00	11.92	+2.53	+1.92	0.919	0.094	0.707	0.801	+0.118	+0.063	1.591	0.734	0.552	1.286	+0.305	+0.154	3.763	4.20	0.323	3.74	+0.02	-0.08	4.00	3.70	0.014	3.71	+0.29	+0.05
xiv	11.15	10.06	1.53	11.59	+2.86	+2.25	0.918	0.077	0.843	0.920	-0.002	-0.057	1.591	0.736	0.647	1.383	+0.208	+0.057	3.763	4.10	0.514	3.95	-0.16	-0.29	4.00	3.88	0.010	3.91	+0.09	-0.14

TABLE XIV
METABOLIC BALANCES, SUBJECT C. O., SEVEN-DAY PERIODS
ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen				Calcium				Phosphorus				Potassium				Sodium														
	Intake	Output			Variation From Control Base-line	Intake	Output			Balance	Variation From Control Base-line	Intake	Output			Balance	Variation From Control Base-line	Intake	Output			Balance	Variation From Control Base-line								
		Urine	Feces	Total			Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total										
Control																															
I.....	14.44	11.30	1.56	12.86	+1.58	-0.08	0.018	0.176	0.690	0.866	+0.052	+0.042	1.623	0.950	0.457	1.407	+0.216	+0.025	3.76	3.52	0.227	3.75	+0.01	-0.06	4.00	3.65	0.013	3.66	+0.34	-0.13	
II.....	14.32	10.48	1.50	11.98	+2.34	+0.68	0.899	0.218	0.719	0.937	-0.038	-0.048	1.590	0.868	0.463	1.331	+0.259	+0.068	3.76	3.30	0.273	3.66	+0.10	+0.03	4.00	3.39	0.015	3.41	+0.59	+0.12	
III.....	14.45	11.93	1.22	13.15	+1.30	-0.36	0.919	0.239	0.612	0.851	+0.008	+0.058	1.591	1.000	0.399	1.399	+0.192	+0.001	3.76	3.68	0.189	3.87	-0.11	-0.18	4.00	3.83	0.011	3.84	+0.16	-0.31	
IV.....	14.45	11.73	1.39	13.12	+1.33	-0.33	0.919	0.212	0.706	0.918	+0.001	-0.009	1.572	0.991	0.459	1.450	+0.122	-0.069	3.76	3.32	0.212	3.53	+0.23	+0.16	4.00	3.32	0.014	3.33	+0.67	+0.20	
Control base-line																															
Average last three weeks	14.41	11.38	1.37	12.75	+1.60	0.0	0.912	0.223	0.679	0.902	+0.010	0.0	1.584	0.953	0.440	1.393	+0.191	0.0	3.76	3.40	0.225	3.69	+0.07	0.0	4.00	3.52	0.013	3.53	+0.47	0.0	
Immobilization in oscillat- ing bed																															
V.....	14.45	11.64	1.36	13.00	+1.45	-0.21	0.919	0.243	0.776	1.019	-0.100	-0.110	1.591	1.006	0.536	1.542	+0.049	-0.142	3.76	3.55	0.262	3.81	-0.05	-0.12	4.00	3.76	0.020	3.78	+0.22	-0.25	
VI.....	14.45	12.60	1.04	13.73	+0.72	-0.94	0.919	0.282	0.594	0.876	+0.043	+0.033	1.591	1.056	0.432	1.488	+0.103	-0.083	3.76	3.55	0.176	3.73	+0.03	-0.04	4.00	3.71	0.020	3.73	+0.27	-0.20	
VII.....	14.45	12.56	1.02	13.87	+0.65	-1.08	0.919	0.306	0.610	0.916	+0.003	-0.007	1.591	1.006	0.420	1.426	+0.165	-0.026	3.76	3.23	0.180	3.41	+0.35	+0.28	4.00	3.52	0.014	3.53	+0.47	0.0	
VIII.....	14.45	12.34	1.35	13.69	+0.76	-0.90	0.919	0.304	0.706	1.010	-0.091	-0.101	1.591	1.038	0.465	1.503	+0.088	-0.103	3.76	2.97	0.218	3.19	+0.57	+0.50	4.00	3.78	0.016	3.80	+0.20	-0.27	
IX.....	14.45	11.70	1.50	13.20	+1.25	-0.41	0.919	0.287	0.779	1.066	-0.147	-0.157	1.572	0.997	0.452	1.449	+0.123	-0.068	3.79	3.16	0.259	3.42	+0.34	+0.27	4.00	3.74	0.015	3.76	+0.24	-0.23	
Average of immobilization	14.45	12.25	1.25	13.50	+0.95	-0.71	0.919	0.284	0.693	0.977	-0.058	-0.068	1.557	1.021	0.461	1.482	+0.105	-0.086	3.76	3.29	0.219	3.51	+0.25	+0.18	4.00	3.70	0.017	3.72	+0.28	-0.19	
Recovery																															
X.....	14.45	11.35	1.63	12.98	+1.47	-0.19	0.918	0.220	0.829	1.049	-0.131	-0.141	1.609	0.911	0.510	1.481	+0.128	-0.063	3.76	3.29	0.273	3.56	+0.20	+0.13	4.00	3.40	0.014	3.41	+0.59	+0.12	
XI.....	14.45	10.60	1.73	12.33	+2.12	+0.46	0.919	0.177	0.709	0.877	+0.042	+0.032	1.572	0.971	0.457	1.428	+0.144	-0.017	3.76	3.24	0.283	3.52	+0.24	+0.17	4.00	3.60	0.026	3.63	+0.37	-0.10	
XII.....	14.45	10.37	1.77	12.14	+2.31	+0.65	0.919	0.152	0.690	0.848	+0.070	+0.060	1.591	0.935	0.474	1.409	+0.182	-0.009	3.76	3.00	0.297	3.30	+0.46	+0.39	4.00	3.50	0.015	3.52	+0.48	-0.01	
XIII.....	14.45	10.03	1.64	11.67	+2.78	+1.12	0.919	0.131	0.612	0.743	+0.176	+0.166	1.591	0.870	0.417	1.287	+0.301	+0.113	3.76	3.32	0.286	3.61	+0.15	+0.08	4.00	3.55	0.017	3.57	+0.43	-0.04	
XIV.....	14.45	9.91	1.65	11.56	+2.89	+1.23	0.918	0.119	0.610	0.729	+0.189	+0.179	1.591	0.859	0.420	1.279	+0.312	+0.121	3.76	3.66	0.326	3.99	-0.23	-0.30	1.00	3.50	0.018	3.61	+0.39	-0.08	

TABLE XV
METABOLIC BALANCES, SUBJECT S. W., SEVEN-DAY PERIODS
ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen				Calcium				Phosphorus				Potassium				Sodium			
	Output				Output				Output				Output				Output			
	Intake	Urine	Feces	Total	Intake	Urine	Feces	Total	Intake	Urine	Feces	Total	Intake	Urine	Feces	Total	Intake	Urine	Feces	Total
Control																				
i*	14.43	12.49	0.94	13.43	+1.00	-0.55	0.919	0.250	0.380	0.630	+0.289	+0.188	1.628	1.040	0.312	1.352	+0.276	+0.087	3.763	10.0
ii	14.43	11.94	0.51	12.45	+0.84	-0.71	0.920	0.285	0.620	0.937	-0.017	+0.118	1.623	1.039	0.575	1.614	+0.009	-0.180	3.763	10.0
iii	14.43	11.86	0.11	11.97	+1.46	-0.09	0.920	0.261	0.533	0.794	+0.126	+0.051	1.626	0.954	0.452	1.406	+0.220	-0.031	3.763	10.0
iv	14.43	11.29	0.52	12.81	+1.62	+0.07	0.920	0.261	0.679	0.933	-0.013	-0.114	1.623	0.919	0.593	1.512	+0.111	-0.078	3.763	10.0
v	14.43	11.60	0.19	12.85	+1.57	+0.02	0.921	0.235	0.496	0.731	+0.190	+0.089	1.604	0.951	0.417	1.368	+0.236	+0.047	3.763	10.0
Control base-line																				
Average last three weeks	14.43	11.61	0.27	12.88	+1.55	0.0	0.920	0.232	0.567	0.819	+0.101	0.0	1.618	0.942	0.487	1.429	+0.189	0.0	3.763	10.0
Immobilization in oscillating bed																				
vi	14.43	11.50	1.33	12.83	+1.54	-0.01	0.920	0.279	0.647	0.925	-0.006	-0.107	1.607	1.064	0.540	1.604	+0.003	-0.186	3.763	10.0
vii	14.48	13.36	1.26	14.62	-0.14	-1.69	0.921	0.355	0.576	0.931	-0.010	-0.111	1.646	1.196	0.517	1.713	-0.067	-0.256	3.763	10.0
viii†	14.70	12.55	1.22	13.77	+0.93	-0.62	0.930	0.403	0.647	1.050	-0.120	-0.221	1.641	1.177	0.507	1.684	-0.043	-0.233	3.763	10.0
ix	14.73	13.16	1.36	14.51	+0.22	-1.33	0.930	0.429	0.679	1.105	-0.174	-0.278	1.680	1.217	0.542	1.750	-0.099	-0.288	3.763	10.0
x	14.70	12.51	1.31	13.85	+0.85	-0.70	0.931	0.445	0.660	1.105	-0.174	-0.275	1.681	1.154	0.509	1.663	-0.025	-0.214	3.763	10.0
Average of Immobilization	14.61	12.63	1.30	13.93	+0.63	-0.87	0.926	0.392	0.642	1.024	-0.098	-0.199	1.639	1.162	0.523	1.685	-0.046	-0.235	3.763	10.0
Recovery																				
xi	14.75	11.93	1.31	13.27	+1.48	-0.07	0.930	0.326	0.689	1.015	-0.085	-0.186	1.682	1.031	0.512	1.543	+0.136	-0.050	3.763	10.0
xii	14.70	10.12	1.36	11.48	+3.22	+1.67	0.931	0.223	0.619	0.842	+0.089	-0.012	1.638	0.947	0.480	1.427	-0.211	+0.022	3.763	10.0
xiii	14.70	10.37	1.20	11.66	+3.04	+1.49	0.930	0.185	0.589	0.774	+0.156	+0.055	1.641	0.919	0.467	1.386	+0.255	+0.066	3.763	10.0
xiv	14.75	11.29	1.22	12.51	+2.24	+0.69	0.931	0.170	0.552	0.719	+0.212	+0.111	1.679	1.004	0.494	1.498	+0.181	-0.008	3.763	10.0
xv	14.70	11.30	1.23	12.53	+2.11	+0.56	0.930	0.147	0.579	0.726	+0.204	+0.103	1.641	0.963	0.529	1.492	+0.149	-0.040	3.763	10.0
xvi	14.72	11.30	1.21	12.51	+2.18	+0.63	0.931	0.150	0.534	0.693	+0.238	+0.137	1.660	0.959	0.483	1.442	+0.218	+0.029	3.763	10.0
xvii	14.70	11.45	1.26	12.71	+1.99	+0.44	0.931	0.185	0.650	0.834	+0.251	+0.180	1.649	0.967	0.447	1.414	+0.235	+0.016	3.763	10.0
New control																				
Base-line for fixed bed ii‡	14.71	11.36	1.24	12.60	+2.11	0.0	0.931	0.160	0.536	0.696	+0.235	0.0	1.650	0.962	0.493	1.455	+0.195	0.0	3.763	10.0
Immobilization, fixed bed																				
ii																				
xviii	14.75	11.89	1.15	13.33	+1.12	-0.69	0.931	0.240	0.551	0.794	+0.137	-0.098	1.679	1.036	0.507	1.543	+0.136	-0.059	3.763	10.0
xix	14.70	13.11	1.45	14.86	-0.16	-2.27	0.930	0.383	0.612	0.995	-0.065	-0.300	1.627	1.191	0.529	1.720	-0.093	-0.288	3.763	10.0
Recovery																				
xx	14.75	11.37	1.53	12.90	+1.85	-0.26	0.931	0.312	0.573	0.884	+0.017	-0.188	1.679	1.052	0.520	1.572	+0.107	-0.088	3.763	10.0
xxi																				

* 5-day period.

† The slight increase in nitrogen, calcium and phosphorus intake beginning at period viii occurred because of the necessity for using "emergency" bread made from dark flour.

‡ 1-day period.

§ Average of periods xv, xvi and xvii.

potassium losses during the first two weeks of immobilization in the oscillating bed at a time when the nitrogen losses were also maximal. Thereafter, despite continued nitrogen losses S. W. and C. O. actually stored potassium; the magnitude of the storage of the potassium by C. O. was such that his overall potassium balance for the entire immobilization period was slightly positive. E. M., on the other hand, lost potassium throughout the immobilization period although there was a decline in his potassium excretion toward equilibrium during the last two weeks.

These variations from subject to subject in potassium excretion during the oscillating bed experiment are pointed up by comparison of the theoretic nitrogen losses based on potassium, employing the ratio given above, with the measured nitrogen losses. In E. M., for example, the theoretic nitrogen loss based on potassium excretion exceeded the actual loss by 115 per cent. In S. W. it was less than the actual nitrogen loss by 46 per cent, in C. O. by 342 per cent. On the other hand, during immobilization in the fixed bed the theoretic nitrogen losses based on potassium excretion exceeded the measured nitrogen losses in all three subjects.

There is no ready explanation for these observed discrepancies between potassium and nitrogen excretion. A potential source of variation in potassium excretion may arise from shifts in body glycogen and intracellular fluid.²⁷ A more likely source for these discrepancies would appear to be irregular variations in the potassium content of the diets. In this study this variable was checked by direct analysis of the dietary intake. Nine analyses of the 2,800 calorie diet carried out during different seasons over the two-year period showed a standard deviation of the potassium values of ± 0.18 Gm. (4.8 per cent).¹³ Although these analyses showed little variation, it is possible that more frequent analyses might have revealed greater variations in diet potassium content. This is suggested by the appearance of occasional simultaneous trends in potas-

sium excretion in the different subjects which were independent of the stage of the experiment. The unreliability of the nitrogen:potassium ratio as a quantitative index of protoplasmic shifts has also been pointed out by other investigators.²⁹

Influence of Oscillating Bed on Calcium Metabolism. Oscillation exerted a striking effect upon the changes in calcium metabolism resulting from immobilization, an effect of considerable interest because of its relation to the problem of urinary tract stone formation in immobilized patients. It had been found in the study of four normal subjects immobilized in fixed beds that the average total urinary calcium excretion was approximately one-half to two-thirds that shown by a group of young men immobilized for four or five weeks because of fracture or osteotomy,³⁰ and the levels of urinary calcium in two of the subjects were well within the range of the fracture group. It had also been shown that during immobilization in the fixed bed certain factors concerned with the solubility of calcium in the urine failed to make appropriate compensatory responses to the increased excretion of calcium. Urinary volume increased very slightly, urinary pH became slightly more alkaline and urinary citric acid, the influence of which in favoring calcium solubility resides in the formation of a weakly ionized and very soluble calcium citrate complex, remained relatively unchanged. This was in contrast to what occurs in the normal ambulatory individual in whom a shift in urine toward the alkaline side and an increase in urinary calcium excretion is regularly accompanied by an increase in urinary citric acid.³¹ The absence of these compensatory responses, the associated increase in urinary phosphorus and the significant increases in urinary calcium during immobilization would all favor the precipitation of calcium phosphatic calculi in the urinary tract. These findings are of considerable interest in view of the rather high incidence of stone formation observed in immobilized patients in service hospitals during the

recent war^{32,33,34} and previously reported by others.^{35,36}

The total loss of urinary calcium during immobilization in the oscillating bed was approximately one-half of that shown by the same subjects immobilized in the fixed bed experiment. The inference that this decrease in calcium loss during immobilization was due to oscillation and not to other factors appeared to be substantiated by the magnitude of the calcium loss which occurred when one of the subjects was immobilized in a fixed bed for a second time. During this re-immobilization of S. W. in a fixed bed for two weeks calcium was lost at the same rapid rate as during his first immobilization in a fixed bed one year previously. Oscillation had no effect upon urinary pH, urinary volume and urinary citric acid. However, in view of the influence of oscillation in reducing the extent of the urinary calcium and phosphorus losses during immobilization this procedure should reduce the hazard of stone formation in the urinary tract during immobilization.

Influence of Oscillation on Circulation. The oscillating bed tended to prevent the deterioration of the mechanisms responsible for circulatory control in the upright position as tested by means of a tilt table. During immobilization in the fixed bed, tilt table tests had demonstrated progressive impairment of circulatory control in the upright position, with an increased tendency to faint, which became pronounced within two to three weeks. In contrast, similar tests carried out during the oscillating bed experiment revealed that control of the circulation in the upright position was maintained almost at control levels throughout the immobilization phase.

Observations during the fixed bed experiment had indicated that the legs were the principal vascular area in which important derangements occurred in the response of the blood vessels to the upright position. Binding the legs to the groin with Acc bandages prevented fainting when the subject stood in the erect position on the tilt table whereas binding of the abdomen was

ineffective. Measurements of the circumference of the legs during tilt table tests had shown greater increases in the size of the legs in the tilted position during the immobilization phase than during the control period. Analysis of the changes in the leg circumference during and after tilting suggested that during immobilization there was impairment of either venous or muscular tone or both. Repetition of these leg measurements during tilt table tests in the oscillating bed experiment revealed that during immobilization, although the subjects stood in the upright position for longer periods of time (as compared with the fixed bed experiment), the increases in the circumference of the legs were not as great. This would suggest that by some mechanism, oscillation tended to prevent impairment of venous or muscular tone in the legs. The occurrence of purpuric hemorrhages in the skin of the legs in tilt table tests during immobilization in the fixed bed and the absence of petechiae in tests during the comparable stage in the oscillating bed experiment would indicate that appreciable capillary wall fragility was prevented by oscillation.

The beneficial effects frequently observed following the use of the oscillating bed in vascular diseases of the lower extremities have been attributed to improvement in blood flow brought about by the motion of the bed. No conclusive evidence for this action has been presented although some attempts have been made to measure peripheral circulation under these conditions. Horton, Krusen and Sheard²⁰ measured skin temperatures during oscillation with equivocal results. The studies of Barker and Roth³⁷ indicated that oscillation raised the skin temperature of the extremities, but their observations were not carried out under carefully controlled environmental conditions. Although the present study did not include direct measurements of blood flow, rhythmic fluctuations in venous pressure as measured in the dorsal vein of the foot were of interest. The venous pressure changed 140 mm. of water with each oscillation of

the bed. The veins could be seen alternately to fill and empty with each oscillation. This may mean that in the presence of competent venous valves a larger volume of venous blood is delivered to the right auricle during oscillation.

Influence of Oscillation on Respiratory Function. Measurements of respiratory function showed a shift in the average level of the diaphragm with each change in position of the bed. This might be regarded as a favorable effect since it would lead to the aeration at intervals of portions of the lungs which would not be aerated at the constant diaphragm level prevailing at rest in a fixed bed. However, the actual volume of pulmonary ventilation per unit of time was not increased by oscillation. The changes in the position of the diaphragm take place gradually over a period of time equal to the cycle of the bed (one and three-quarter minutes in this experiment).

Of some interest in relation to the possible use of the oscillating bed with cardiac patients was the finding that oscillation at the speed employed did not increase the metabolic rate over that in the resting horizontal position. Subsequent studies on other patients have confirmed this finding.

Blood Coagulation Mechanism. It is worthy of emphasis that no increased tendency for the blood to coagulate during immobilization was found in either the fixed or oscillating bed experiments. In particular, prior to and during the re-immobilization of subject S. W. in a fixed bed an increased number and variety of tests were employed (heparin tolerance test weekly, prothrombin time determinations every other day, and Lee-White and capillary tube coagulation times every other day) without the detection of significant alterations in the blood coagulation mechanism.

Effect of Oscillation on Recovery from Immobilization. The restoration of metabolic and physiologic indices to normal came about more rapidly following immobilization in the oscillating than in the fixed bed. Physiologic function returned to normal more promptly than did the metabolic.

Indeed, the delay in the return to normal of metabolic function in both experiments should be emphasized. In neither experiment had the nitrogen and calcium metabolism fully reverted to control levels during the recovery periods of four to six weeks. There was also considerable individual variability in the speed of recovery. The somewhat more rapid improvement in nitrogen and calcium balances during recovery in the oscillating bed experiment was attributable to at least three factors: (1) The balances were less negative during immobilization in the oscillating bed and hence a smaller shift was required to reach a positive balance. (2) The immobilization phase in the oscillating bed experiment was one to two weeks shorter; hence the aggregate of the catabolic changes was considerably less than in the fixed bed experiment. (3) The subjects were psychologically ready for and initiated mobile activity three days earlier in the oscillating bed recovery period. These modifying factors may in part account for the fact that most physiologic functions (basal metabolic rate, muscle strength, girth of extremities, the reaction of the circulation to the erect position, exercise tolerance and the reclining pulse rate) returned to control levels from one to two weeks earlier in the recovery phase following immobilization in the oscillating than in the fixed bed.

Repetition of Fixed Bed Experiment. At the conclusion of the oscillating bed experiment subject S. W. was immobilized in a fixed bed for a second time in order to provide a check on the results of the previous fixed bed experiment. This procedure would also test the validity of the conclusion that the differences in the results of the fixed and oscillating bed experiments were specifically due to oscillation and not to any interval change in the condition of the patient. During this two weeks of re-immobilization in a fixed bed the metabolic and physiologic derangements which occurred duplicated very closely in pattern and extent the changes which had occurred during the first two weeks of this subject's first im-

mobilization in a fixed bed a year previously. In most respects the changes were significantly greater than had occurred during the first two weeks of his antecedent immobilization in an oscillating bed. The differences in the results of the fixed bed and oscillating bed experiments are therefore attributable to the modifying effects of oscillation rather than to changes in the subject's growth, development or physical condition.

Mechanism of Action of Oscillating Bed. The mechanism by which the oscillating bed serves to ameliorate the effects of immobilization is not clear. It is believed that the principal factors may be an increased circulation through the extremities and partial weight-bearing in the foot-downward position. The rocking motion of the bed which places the legs alternately in a dependent position and in a slightly elevated position is identical in principle to Buerger's postural exercises, long in use in the treatment of conditions resulting from defective peripheral circulation. The oscillating bed is superior to Buerger's exercises, however, in that the changes in posture can be repeated continuously for many hours without physical effort on the part of the subject or patient. In regard to weight-bearing it is evident from actually experiencing the motion of the bed that if a foot-board is used or the legs and feet enclosed in a cast, partial weight-bearing definitely occurs provided the bed is tilted to a sufficient angle. This action probably transmits some stress or strain to the body, particularly to the skeleton, and also brings about slight muscular contraction, principally in the gastrocnemius-soleus and quadriceps muscle groups. Muscular contraction *may* in turn call for greater blood flow. It is conceivable that skeletal stress and the stimulation to slight muscular contraction may act to discourage catabolic and encourage anabolic processes.

It is to be noted that in this experiment oscillation was begun at the start of the immobilization period. Whether or not oscillation would reduce metabolic losses

once they become well established cannot be determined from this experiment.

It is uncertain what the optimal daily period for oscillation should be. In one of the subjects the oscillating bed was in motion twenty-one hours a day; in the other two subjects, E. M. and C. O. who were studied together, the bed was in motion eight hours daily because of the fact that two oscillating beds were not exclusively available during the period of the experiment. There was no evidence that the longer period of oscillation was more effective.

CONCLUSIONS

It seems reasonable to conclude from these findings that the oscillating bed may in considerable measure prevent many of the deleterious effects consequent upon prolonged immobilization. These beneficial effects are exerted on the mechanism responsible for circulatory control in the erect position, on the changes in muscle mass and strength and on creatine, nitrogen, calcium and phosphorus metabolism. The metabolic effects exerted by oscillation would serve to reduce the likelihood of calculus formation in the urinary tract. The oscillating bed is a simple and practical device, readily available, generally comfortable and capable of saving considerable nursing and physiotherapeutic care. On the basis of these findings it seems reasonable to suggest that the oscillating bed may provide a valuable adjunct in the management of patients immobilized for long periods because of fractures, severe burns, spinal cord injuries or paralysis resulting from poliomyelitis. This suggestion is made with the reservation that the beneficial effects of oscillation on physiologic and metabolic functions in immobilized healthy adults may not necessarily occur in diseased states. This uncertainty can be resolved only by direct experimental trial.

SUMMARY

A study was made of the influence of an oscillating bed on the metabolic and

physiologic disturbances associated with immobilization. The subjects were three normal healthy young men. The investigation was carried out on a metabolism ward during control (four to five weeks), immobilization (five weeks) and recovery (five to six weeks) periods. The dietary intake was constant. During the immobilization periods the subjects were in bivalved plaster casts extending from umbilicus to toes. One year previously the three subjects studied had participated in an experiment identical with the present study except that they had been immobilized in standard (fixed) hospital beds. During immobilization in the oscillating bed:

1. Nitrogen excretion increased in the same general pattern as in the fixed bed experiment; but in two of the subjects nitrogen loss was approximately half as great as during an equal period of immobilization in the fixed bed.

2. The loss of calcium, chiefly in the urine, was, on the average, half as great as during the same period in the fixed bed.

3. The loss of phosphorus was significantly less in two of the subjects than during the same period in the fixed bed.

4. Although urinary citric acid, pH and urine volume did not appreciably change, the significant reduction in urinary calcium and phosphorus losses would render the precipitation of calcium phosphate in the urinary tract less likely than during immobilization in a fixed bed.

5. There was good correlation between the excretion of urinary total sulfur and nitrogen on the basis of the ratio in which they exist in muscle. The correlation between nitrogen and phosphorus on the same basis was less good, between nitrogen and potassium poor.

6. Creatine tolerance tests indicated that creatine metabolism was significantly less impaired than during immobilization in the fixed bed. The decrease in muscle mass and strength of the immobilized limbs was also less than during an equal period in the fixed bed.

7. Changes in basal oxygen consumption were not significant.

8. The deterioration produced by fixed bed immobilization in the mechanisms essential for adequate circulation in the erect position (as measured by tilt table tests) was largely prevented.

9. Measurements of venous pressure in the foot veins during oscillation revealed an average change in pressure of 140 mm. of water with each change in position of the bed. A rhythmical shift was observed in the average level of the diaphragm with each change in position of the bed; without significant alteration in the pulmonary minute ventilation.

10. Changes in urinary 17-ketosteroid excretion and in serum calcium levels were not significant.

11. As in the fixed bed experiment, there were no significant alterations in blood coagulation studies, circulation time, heart size or electrocardiograms.

During the recovery phase most metabolic and physiologic functions returned to control levels or became re-stabilized more rapidly than following immobilization in the fixed bed.

Following recovery from the oscillating bed experiment, one subject was re-immobilized in a fixed bed for two weeks. The results duplicated closely the changes observed during the first two weeks of his first immobilization in a fixed bed a year previously.

The authors wish to express their deep appreciation to Miss Hertha H. Taussky of this department for her direction of the citric acid studies in this and the previous report.

REFERENCES

1. DEITRICK, J. E., WHEDON, G. D. and SHORR, E. The effects of immobilization upon various metabolic and physiologic functions of normal men. *Am. J. Med.*, 4: 3, 1948.
2. NEWBURGER, B. Early post-operative walking. II. Collective review. *Surgery*, 14: 142-154, 1943.
3. LEITHAUSER, D. J. Confinement to bed for only 24 hours after operation. *Arch. Surg.*, 47: 203, 1943.
4. POWERS, J. H. The abuse of rest as a therapeutic measure in surgery. *J. A. M. A.*, 125: 1079, 1944.
5. CANAVARRO, K. Early post-operative ambulation. *Ann. Surg.*, 124: 180, 1946.

6. HELLEBRANDT, F. A. Adaptability of present day concepts of convalescent training and physical rehabilitation to the civilian practice of medicine. *Arch. Phys. Med.*, 27: 136, 1946.
7. MUELLER, V. A., JR. and SILVERMAN, L. K. Experiment in physical reconditioning at Camp Crowder. *War Med.*, 7: 365, 1945.
8. RUSK, H. A. The Army Air Forces convalescent training program. *South. M. J.*, 38: 12, 1945.
9. RUSK, H. A. Convalescent care and rehabilitation in the Army Air Forces. *M. Clin. North America*, p. 715, May, 1945.
10. LIPPMAN, R. W. Medical implications of convalescence. *Arch. Phys. Med.*, 27: 477, 1946.
11. SANDERS, C. E. Cardiovascular and peripheral vascular diseases; treatment by a motorized oscillating bed. *J. A. M. A.*, 106: 916, 1936.
12. TOSCANI, V. Comparison of analyzed with calculated diets. *Food Research*, 13: 187, 1948.
13. TOSCANI, V. and BUNIAK, V. Sodium and potassium content of meats. *Food Research*, 12: 328, 1947.
14. TAUSKY, H. H. and SHORR, E. A microcolorimetric method for the determination of citric acid. *J. Biol. Chem.*, 169: 103, 1947.
15. DE TAKATS, G. Heparin tolerance; a test of the clotting mechanism. *Surg. Gynec. & Obst.*, 77: 31, 1943.
16. SHAPIRO, S., SHERWIN, B., REDISH, M. and CAMPBELL, H. A. Prothrombin estimation: a procedure and clinical interpretations. *Proc. Soc. Exper. Biol. & Med.*, 50: 85, 1942.
17. BARKER, N. W. Use of oscillating beds in treatment of peripheral occlusive arterial disease. *Proc. Staff Meet., Mayo Clin.*, 14: 618, 1939.
18. WRIGHT, I. S. Conservative treatment of occlusive arterial disease. *Arch. Surg.*, 40: 163, 1940.
19. WARSHAWSKY, H. and DEMPSEY, M. W. The physical therapy of peripheral vascular disease. *Arch. Phys. Therapy*, 24: 487, 1943.
20. HORTON, B. T., KRUSEN, F. H. and SHEARD, C. An evaluation of methods and mechanical devices used in the treatment of peripheral vascular diseases. *Arch. Phys. Therapy*, 22: 389, 1941.
21. DURYEE, A. W. The management of peripheral vascular disease. *Bull. New York Acad. Med.*, 19: 478, 1943.
22. DURYEE, A. W. Thrombophlebitis—medical treatment. *Bull. New York Acad. Med.*, 20: 604, 1944.
23. ALBRIGHT, F. Cushing's syndrome. Its pathological physiology, its relationship to the adreno-genital syndrome, and its connection with the problem of the reaction of the body to injurious agents ("alarm reaction" of Selye). The Harvey Lectures, series xxxviii: 123, 1942-1943.
24. SHOHL, A. T. Mineral Metabolism. P. 19. New York, 1939. Reinhold Publishing Corp.
25. KATZ, J. Die mineralischen Bestandtheile des Muskelfleisches. *Arch. f. d. ges. Physiol.*, 63: 1, 1896.
26. HOWLAND, J., MARRIOTT, W. M. and KRAMER, B. Studies upon the inorganic composition of bones. *J. Biol. Chem.*, 68: 721, 1926.
27. REIFENSTEIN, E. C., JR., ALBRIGHT, F. and WELLS, S. L. The accumulation, interpretation, and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen. *J. Clin. Endocrinol.*, 5: 367, 1945.
28. HARRISON, H. E., DARROW, D. C. and YANNET, H. The total electrolyte content of animals and its probable relation to the distribution of body water. *J. Biol. Chem.*, 113: 515, 1936.
29. HOWARD, J. E. Conference on metabolic aspects of convalescence, sponsored by the Josiah Macy, Jr. Foundation. Fifth meeting. Pp. 33-38, October 8-9, 1943.
30. HOWARD, J. E., PARSON, W. and BIGHAM, R. S., JR. Studies on patients convalescent from fracture. III. The urinary excretion of calcium and phosphorus. *Bull. Johns Hopkins Hosp.*, 77: 291, 1945.
31. SHORR, E., ALMY, T. P., SLOAN, M. H., TAUSKY, H. H. and TOSCANI, V. The relation between the urinary excretion of citric acid and calcium; its implications for urinary calcium stone formation. *Science*, 96: 587, 1942.
32. JOELSON, MAJOR J. J. Quoted by J. E. Howard.³⁰
33. LEADBETTER, W. F. and ENGSTER, H. C. The problem of renal lithiasis in convalescent patients. *J. Urol.*, 53: 269, 1945.
34. FETT, H. C. and KANE, J. T. Urinary calculi in recumbent fracture patients. *Am. J. Surg.*, 71: 441, 1946.
35. FLOCKS, R. H. Calcium phosphate renal lithiasis. *J. Iowa M. Soc.*, 35: 321, 1945.
36. WILSON, W. E. Renal colic and hematuria following recumbency. *Brit. M. J.*, 2: 101, 1931.
37. BARKER, N. W. and ROTH, G. M. The treatment of occlusive arterial disease of the legs by means of the Sanders vasoscillator (Sanders bed). *Am. Heart J.*, 18: 312, 1939.

Effect of Vomiting Due to Intestinal Obstruction on the Serum Potassium*

Chemical and Electrocardiographic Observations in Fifteen Cases Preliminary Report

SAMUEL BELLET, M.D., CARL S. NADLER, M.D., PETER C. GAZES, M.D.
and MARY LANNING, B.S.
Philadelphia, Pennsylvania

UNTIL recently alkalosis accompanying vomiting was commonly regarded as being associated with the balance of sodium and chloride in extracellular fluids and little significance was attached to incidental changes in other electrolytes and in the ionic constitution of the cells themselves. Recently the reports of Butler,¹ Fenn,² Darrow,^{3,4} Talbott,⁵ Gamble⁶ and others have called attention to the alterations in the intracellular as well as extracellular fluid which occur during alkalosis and the acidosis which accompanied loss of fluids from the body. Specifically, it has been shown that sodium may pass from the extracellular fluid into the cells and replace potassium. Darrow³ has shown that there is a marked loss of potassium accompanying states associated with dehydration, particularly diarrhea in infants. Similar losses of potassium have also been shown to occur in other conditions to be discussed later.

✓In 1938 Scudder and associates⁷ studied a series of twenty untreated patients with intestinal obstruction and found the serum potassium to be raised in seven, low in five and normal in eight. They also found that the cellular potassium in these untreated patients was low in fourteen of the twenty. Falconer^{8a,b} (1939) was unable to verify that either hypopotassemia or hypercalce-

mia were factors in intoxication accompanying intestinal obstruction. He found that there was a tendency for the concentration of potassium, sodium and calcium in the serum to decrease, the reduction in potassium tending to be relatively the largest.✓

In view of these observations, and more particularly because we were struck by the similarity of the electrocardiographic changes associated with intestinal obstruction to those of hypopotassemia in other conditions, we decided to study the electrocardiographic findings in intestinal obstruction accompanied by vomiting, to compare the electrocardiographic changes with the levels of serum potassium and to determine the effect of administration of potassium upon these changes. We wish to report our observations on the electrolyte changes, particularly as they concern the serum potassium, in fifteen cases of acute intestinal obstruction. Since we wish to emphasize the value of the electrocardiograph, not only in detecting the presence of hypopotassemia in intestinal obstruction but also in following, in a rough way, the fluctuations of the serum concentration of this electrolyte, the electrocardiographic findings in hypopotassemia will be briefly discussed before the details of our observations are presented.

* From the Division of Cardiology and Chemistry, Philadelphia General Hospital and Robinette Foundation, University of Pennsylvania, Philadelphia, Pa. This work was aided by a grant from the United States Public Health Service.

ELECTROCARDIOGRAPHIC CHANGES
ASSOCIATED WITH LOW SERUM
POTASSIUM

The electrocardiographic findings in hyperpotassemia are quite well established.^{9a-e} The characteristic tall, narrow T waves,

seventy years of age or older, five were between sixty and seventy, three were between fifty and sixty and three were between twenty-five and fifty years of age. The series consisted of nine men and six women. Thirteen patients were white and two were negroes. The diagnoses

TABLE I
SERUM CONCENTRATIONS, CASE 9
C. J., aged seventy; diagnosis: carcinoma of colon.

Date	K (mEq./L.)	Na (mEq./L.)	Ca (mEq./L.)	Chloride (mEq./L.)	CO ₂ (mEq./L.)	Urea (mg. %)	Remarks
1/6/48	3.6	140	4.4				
1/7/48	2.8	149	4.9				
1/8/48	3.3	137	4.9	85	27		
1/9/48	2.5	138	4.3				
1/10/48							
2:30 P.M.	2.9	139	4.7	Before KCl
4 P.M.	4.5	140	4.3	94.2	After 500 ml. KCl i.v.
11 P.M.	3.8	132	6½ hr. after KCl
1/12/48	3.8	117	4.9	..	45	100	
1/14/48	2.7	129	4.5	74	17		
1/15/48	2.9	132	..	69	21	70	
1/21/48	3.8	137	4.1	86	..	30	
2/5/48	5.4	140	5.3				

often accompanied by some widening of the QRS complexes, are reversible and give way to normal waves as the hyperpotassemia becomes lowered toward normal. The electrocardiographic alterations associated with a low serum potassium have received less study. In 1937 Bellet and Dyer¹⁰ reported characteristic electrocardiographic changes in twenty-three patients after their emergence from diabetic acidosis. These changes consisted of a lengthening of the Q-T interval, depression of the S-T segment and, in some instances, inversion of the T waves. The relation of these changes to hypopotassemia was not established at that time. However, the relationship of characteristic electrocardiographic changes in hypopotassemia and in diabetic acidosis has been well established by the more recent studies of Holler,¹² Nicholson and Branning, Martin and Wertman¹³ and Nadler, Bellet and Lanning.¹⁴

MATERIAL AND METHOD OF STUDY

The ages of our patients ranged from twenty-five to eighty-seven years; four patients were

were: Duodenal ulcer with pyloric obstruction in four patients; carcinoma of the large bowel with intestinal obstruction in three patients; obstructing carcinoma of the stomach in two patients; strangulated hernia in one patient and cholelithiasis with peritonitis and intestinal obstruction in one patient.

As one would anticipate most of these patients were quite ill on admission. They manifested varying degrees of dehydration through loss of fluid by vomiting and in addition, in a few patients, by diarrhea. Mental symptoms ranging from disorientation to coma were observed in some and many presented the picture of shock.

As soon as possible after admission and diagnosis blood was drawn and estimations made of the serum potassium, sodium and calcium, the CO₂ combining power and plasma chloride. These studies were instituted before therapy in five patients (Cases 9, 10, 13, 14 and 15) and after treatment had been started in the ten remaining patients. These chemical studies were repeated at frequent intervals during the continuance of therapy until the patient recovered or died. Most of these patients received parenteral fluids in the form of normal saline solution, 5 per cent glucose, blood transfusions and

amigen. In addition Wangenstein suction was instituted in many of these patients. Electrocardiograms (limb leads I, II and III and pre-cordial leads CR₃, CR₄ and CR₅) were taken at the same time that blood samples were obtained. In five patients calcium in the form of

patients. In the five of the fifteen patients who had not received therapy prior to the initial estimation the serum potassium was also low. In general the level of serum potassium varied with the degree of alkalosis; the greater the degree of alkalosis the

TABLE II
SERUM LEVELS, CASE 15
J. G., aged twenty-five, diagnosis: ruptured duodenal ulcer.

Date	K (mEq./L.)	Na (mEq./L.)	Ca (mEq./L.)	Cl (mEq./L.)	CO ₂ (mEq./L.)	Protein (Gm. %)	Blood Urea Nitrogen (mg. %)	Intake Record
2/5/48	2.7	147	4.7	72	39	5.7	150	3,000 cc. 5% glucose in saline
2/6/48	2.3	150	...	79	35	...	150	1,890 cc. tea and water orally
	3.7	98	34 before KCl 35 after KCl	...	105 before KCl 95 after KCl	7:30 A.M., 1,000 cc. 5% glucose in saline 10:30 A.M. 200 cc. 19% glucose in water From 7 to 4 P.M. 2,100 cc. tea orally, H ₂ O and jello 8 P.M. 500 cc. KCl 10 P.M. 700 cc. amino acids Clinically improved
2/7/48	2.7	142	4.0	80	31	...	90 12 hr. after KCl	2,000 cc. 10% glucose in H ₂ O 1,000 cc. 5% glucose in saline 1,000 cc. amigen 3,130 cc. tea and water Clinically improved
2/8/48	29	Fluids orally 4,280 cc. tea and water
2/9/48	77	26	...	31	Fluids orally 3,780 cc. tea, H ₂ O, milk
2/10/48	4.5	140	4.7	...	26	...	39	Fluids orally 4,160 cc. tea, H ₂ O, milk; patient sitting up

10 cc. of 10 per cent calcium gluconate was injected intravenously prior to administration of potassium in order to determine whether deficiency of this ion was responsible for the electrocardiographic changes. In the series of patients with intestinal obstruction we satisfied ourselves that potassium, not calcium, deficiency was the cause of the electrocardiographic changes by showing that the serum calcium was not low and that intravenous calcium had no effect upon the electrocardiogram while serum potassium was low in five patients and its intravenous administration did return the tracings toward normal. The blood pressure was recorded at frequent intervals prior to, during and following administration of potassium.

The serum sodium and potassium concentrations were measured by means of the flame photometer.¹⁵ (Tables I, II and III.)

FINDINGS

Serum Potassium and Other Electrolyte Values.

The serum potassium on or soon after admission ranged between 2.3 mEq./L. and 2.5 mEq./L. in four patients and between 2.5 and 4.1 mEq./L. in eleven

lower the serum potassium. In practically all of these patients the serum potassium dropped to still lower levels following parenteral therapy which did not include potassium. The pertinent clinical findings, serum potassium levels, electrocardiographic findings on admission and the results of therapy are shown in Table IV.

The serum sodium, chloride and bicarbonate values in our series of patients differed in no way from the well known changes produced by vomiting due to intestinal obstruction. The resulting concentrations in the plasma depended upon the site of the intestinal obstruction (whether high or low), the duration and severity of the vomiting and the accompanying degree of dehydration. In general, in the presence of high intestinal obstruction the chief alterations observed were a marked diminution in chlorides, a slight or moderate diminution in sodium and an increase in carbon dioxide combining power with evidence of alkalosis. In low intestinal

obstruction there was moderate diminution in chlorides and, frequently, a marked loss of sodium with a tendency toward acidosis. The administration of parenteral fluids (saline and glucose) when the patient took no food by mouth resulted in an increase

ranged between 3.5 to 4.5 mEq./L. in most of our patients when the serum potassium was low. This decrease involved the ionized as well as the unionized fraction.

Effect of Administration of Potassium on the Clinical State of Patient. Potassium chloride

TABLE III
SERUM LEVELS, CASE 10
J. McC., aged thirty-four, diagnosis, acute pancreatitis, pyloric obstruction.

Date	K (mEq./L.)	Na (mEq./L.)	Ca (mEq./L.)	Chloride (mEq./L.)	CO ₂ (mEq./L.)	Remarks
12/29/47	3.6	140	51	
12/30/47	2.0	149	3.8			
12/31/47						
4:15 P.M.	2.8	147	4.5	..	35	After 200 cc. KCl
5 P.M.	2.8	142	4.6	76		
1/8/48	2.8	138	4.3	71	36	
1/9/48	3.6	132	4.8	83	38	
1/14/48						
12:30 P.M.	2.7	150	4.9	After 300 cc. KCl
2 P.M.	4.3	141	4.8			
1/15/48	3.5	138	...	76	24	
1/21/48	3.7	141	4.9	79	29	
2/5/48	2.4	144	3.9			
2/6/48	2.3	149	4.2			
2/7/48	2.3	147				
2/11/48	1.7	143	4.4	59	45	
2/12/48	2.3	130	4.4			
2/13/48	2.0	138	4.7	63	53	
2/16/48	1.9	...	6.7	69	45	
2/17/48	1.7	67	41	
2/18/48	1.7	146	...	66	56	
2/19/48	2.2	150	...	67	51	
2/20/48	2.3	142	3.7	70	50	
2/21/48	2.3	142	3.8	72	42	
2/22/48	2.0	141	3.8	71	36	
2/23/48	2.0	142	4.1	72	40	

in chlorides, with a tendency for the degree of alkalosis to diminish. However, on administration of fluids which did not contain potassium the serum potassium tended not only to remain low but to fall below the initial values present on admission.

Of particular interest was the relationship between the level of the serum calcium and the serum potassium. When the serum potassium values were quite low (1.7 to 3.3 mEq./L.), usually associated with a considerable degree of alkalosis, the serum calcium levels also tended to be low but not nearly so low proportionately as the serum potassium. The serum calcium levels

in the form of a 1.14 (isotonic) per cent solution was administered twelve times to ten patients. The dosage ranged from 100 to 700 cc. administered over a period of one-half to two and one-half hours. The effects upon the serum potassium are shown in Table v. Electrocardiograms were taken almost continuously during its administration in most of these patients. Following injection these patients in many instances showed evidence of clinical improvement as manifested by diminished weakness and a sense of well being. The blood pressure, usually low prior to injection, often rose 30 to 40 mm. Hg after potassium had been

TABLE IV

Case No.	Name	Age	Diagnosis	Vomiting (days)	Condition on Admission	Initial ECG	Initial Serum Potassium (mEq./L.)	Effect of Potassium on ECG and Serum Potassium	Ultimate Outcome
1 White Female	K. T.	70	Large bowel obstruction; strangulated femoral hernia	4	Dehydrated; weak	Prolonged QT; ST depression	2.4	Not given	Died
2 Negro	J. J.	57	Ulcer of duodenum with pyloric obstruction	4	Weak, comatose	Prolonged QT; ST depression	2.5	150 cc. in $\frac{1}{2}$ hr.; decreased QT; ST returned to isoelectric line; K rose to 3.08 mEq./L.	Improved
3 White Female	C. L.	66	Cholecystitis; perforation of gallbladder; right subdiaphragmatic abscess	4	Acutely ill; abdominal distention; pain; rigidity of right upper quadrant	Prolonged QT; ST depressed	2.85	500 cc. of KCl in 1 hr.; K rose to 4.08 mEq./L. QT decreased, ST normal	Died
4 White Female	A. S.	72	Intestinal carcinoma with pyloric obstruction	1 wk.	Dehydrated; weak	Depressed ST; prolonged QT	3.6	Returned to normal	Signed out against advice
5 White Female	E. H.	65	Carcinoma of sigmoid with metastasis to liver	2	Dehydrated; weak; disoriented	Prolonged QT; depressed ST	3.4	Returned to normal	Discharged; condition improved
6 White Male	B. W.	68	Pyelonephritis with adynamic ileus	2	Dehydrated; weak; cyanosis; rapid pulse; shallow respirations; rigidity in abdomen; peristalsis	Inverted T wave with prolonged QT	3.3	Given 150 cc., T waves in CR, less inverted, K rose to 3.33 mEq./L.	Died
7 White Male	G. H.	61	Perforation of stomach due to ulcer; subphrenic abscess; generalized peritonitis with localization; arteriosclerotic heart	3	Fever; weakness	Depressed ST; prolonged QT	3.6	QT decreased; ST segment depressed; extrasystoles disappeared; K rose to 5.0 mEq./L.	Died
8 White Female	L.	61	Mentally defective; choledochotomy; removal of stone in common duct	?	Abdominal pain; dehydrated; clay-colored stools; icteric; tenderness in right upper quadrant	Depressed ST; prolonged QT	4.1	Returned to normal	Discharged improved
9 White Male	J. C.	76	Carcinoma of splenic flexure	1 wk.	Pain in lower abdomen; vomiting	Depressed ST; prolonged QT	2.9	QT returned to normal; ST depression disappeared; K rose to 5.13 mEq./L.	Improved
10 White Male	J. M.	45	Cysts of pancreas; pyloric stenosis	3 wk.	Dehydrated; weak	Depressed ST; prolonged QT	2.8	Short QT with up-right T wave; after 200 cc. K rose to 2.95 mEq./L.	Improved
11 White Male	P. W.	63	Gastric carcinoma	3 wk.	Pain in upper abdomen; emaciated; not acutely ill	Prolonged QT; inverted T wave	3.2	Less T wave inversion; after 300 cc. K rose to 4.61 mEq./L.	Died after operation
12 Female	W. J.	51	Carcinoma of fundus; hysterectomy; shock after operation; parenteral fluid	2	Shock; dehydrated	Prolonged QT	2.4	Return to normal	Improved
13 White Female	C. W.	42	Duodenal ulcer with pyloric obstruction	1 mo. also 1 to 2 watery stools per day	Dehydrated undernourished	Inverted T wave in all leads; long QT	3.8	Return to normal after 500 cc. K rose to 4.61 mEq./L.	Discharged improved
14 White Male	G. S.	87	Fracture of femur; intestinal obstruction	4	Dehydrated; weak	Prolonged QT; inverted T wave in all leads	3.9	Return to normal; after 500 cc. K rose to 6.66 mEq./L.	Discharged improved
15 White Male	W. G.	25	Ruptured duodenal ulcer	1	Shock; dehydrated	Low T ₂ and U wave; long QT	2.3	Return to normal, after 500 cc. K rose to 3.2 mEq./L.	Improved

given. The diastolic pressure usually increased more than the systolic. The improvement was only temporary unless the cause for the potassium deficit was removed or the patient began to take food by mouth. In two of these patients (Cases 14 and 15) administration of potassium initiated improvement of the patient which was manifested by diminution of azotemia, a desire to take food by mouth, rapid return of the electrolytes to normal and recovery of the patient. The effects upon the electrocardiograph will be discussed presently.

Effect of Potassium Administration on the Level of Serum Potassium in Hypopotassemia. In Table II the effects of potassium chloride on the level of the serum potassium are noted. It will be observed that with small doses of potassium chloride, 125 to 150 cc., the rise in the level of the serum potassium at the end of administration was not very great. With larger doses (300 to 700 cc.) increase in the serum potassium level was greater and ranged up to 2.8 mEq./L. above the control level.

Effect of Administration of Potassium on Electrocardiogram in Hypopotassemia. Prior to administration of potassium the effect of intravenous administration of calcium gluconate (10 cc. of a 10 per cent solution) was noted. This had no appreciable effect on the T waves and the S-T segments in the five patients to whom this was given, thereby showing that the electrocardiographic changes were not the result of calcium deficiency. Following administration of potassium, the depression of the S-T segments diminished, the T waves tended to become or actually became upright and the Q-T segments were shortened in every case. (Figs. 1, 2, 3 and 4.) The degree of return to normal depended upon the degree of hypopotassemia present prior to injection and the amount of electrolyte administered. When small doses of potassium were given (100 to 200 cc.), only a partial return to normal occurred. With larger doses, a complete return to a normal tracing was observed. Extrasystoles which were present in five cases with low potassium were

abolished following administration of this electrolyte.

The electrocardiographic improvement following administration of potassium was temporary in some patients; in others some degree of improvement persisted. In about

TABLE V

Case No.	Initial Serum Potassium (mEq./L.)	Quantity of 1.14 Per Cent Potassium Chloride per Unit Time Given	Serum Potassium at End of Administration (mEq./L.)
2	2.5	150 cc. in $\frac{1}{2}$ hour	3.3
3	2.85	500 cc. in 1 hour	4.08
4	3.6	125 cc. in 1 hour	4.1
6	3.3	100 cc. in 1 hour	3.7
7	3.6	150 cc. in 1 hour	5.1
8	4.1	150 cc. in 1 hour	4.1
9	2.9	500 cc. in 2 hours	4.5
10	2.8	150 cc. in 1 hour	2.9
10	2.7	300 cc. in 2 hours	4.3
11	3.7	200 cc. in 2 hours	3.8
11	3.2	300 cc. in 2 hours	4.5
13	3.8	300 cc. in 2 hours	4.5
14	3.8	700 cc. in 3 hours	6.6
15	2.3	500 cc. in 2 hours	3.7

one-half to three hours following administration the changes tended to revert to their previous configuration although in some instances some degree of improvement in the T waves and S-T segment was preserved. (Figs. 2, 3 and 4.)

COMMENTS

A study of the literature together with an analysis of the data in our patients indicates that profound electrolyte disturbances are observed during acute intestinal obstruction. In addition to loss of water there is considerable depletion of body potassium. Marked diminution in body potassium results in precipitation of the syndrome of hypopotassemia. This electrolyte cannot be restored by administration of saline and glucose solutions and can be supplied only by direct administration or by food containing potassium.

RECOGNITION OF POTASSIUM DEFICIENCY

The diagnosis of potassium deficiency depends upon (1) recognition of the con-

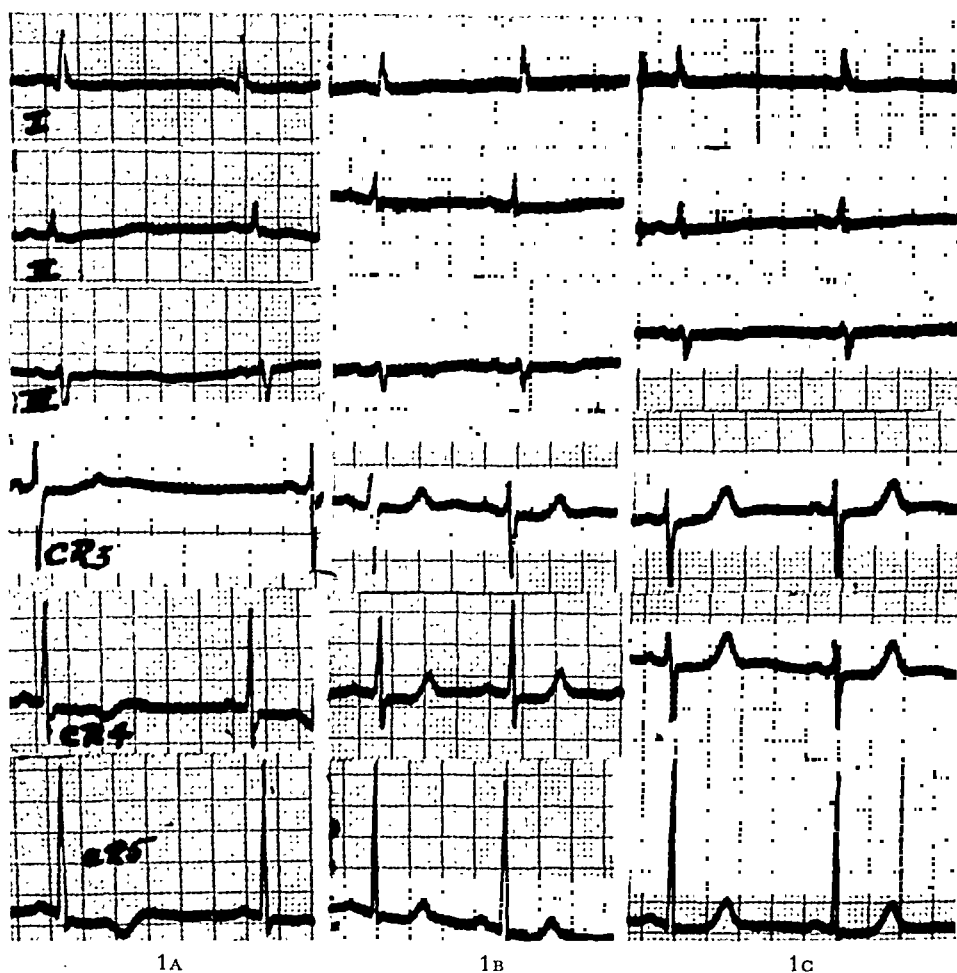


FIG. 1. C. L., a white patient aged sixty-six. A, electrocardiogram taken January 19, 1948, after the patient had been vomiting four days. Note inverted T wave in lead I, ST depression with prominent U wave in lead II and Lead III and inversion of the T wave in CR₃ and CR₅ with depression of the RT segment. The serum potassium at this time was 2.85 mEq./L. B, after 250 cc. of isotonic potassium chloride had been administered in a period of one hour and fifteen minutes. Note flattening of the T wave in leads I and II. Note that the T waves in CR₃, CR₄ and CR₅ are now upright. C, after 500 cc. potassium chloride had been given in two and one-half hours. Note flattening of the T wave in lead I with a tendency to an upright configuration, flattening of the T wave in lead II, with upright T waves in CR₃, CR₄ and CR₅. The potassium at this time was 4.08 mEq./L. The blood pressure rose from the control value of 100/80 to 120/90 after administration of potassium chloride.

ditions likely to be associated with this disturbance; (2) the presence of muscular weakness and atonic muscles and occasionally muscular paralysis; (3) characteristic electrocardiographic changes which return to normal when potassium is given; (4) confirmation by determination of the serum potassium. Particularly important is an estimation of the loss of body potassium by measurement of the retention of this electrolyte during the state of recovery.

In man, hypokassemia has been studied

chiefly in familial periodic paralysis. In these patients muscle weakness, difficulty in respiration due to paralysis of the accessory muscles of respiration, general muscular paralysis and even death has been noted. More recently similar phenomena have been observed following therapy in diabetic acidosis and in chronic nephritis in which the serum potassium level may be as low as 2.0 mEq./L. While marked degrees of muscular paralysis are relatively uncommon accompaniments of potassium

deficiency, minor and moderate degrees of muscular weakness are common. In a recent paper Huang and Mao¹⁶ describe eleven cases of transient paralysis occurring in patients with cholera on the second to ninth day after hospital admission. The paralysis was regarded as analogous to that developing in familial periodic paralysis and responded dramatically to the intravenous injection of potassium chloride. Unfortunately, the authors were unable to determine the level of serum potassium.

While no instance of frank muscular paralysis was observed in the patients in our series, varying grades of muscular weakness and asthenia were present. These were, in many instances, improved following administration of potassium. It is suggested that mild and moderate grades of muscular weakness and asthenia resulting from hypopotassemia are probably overlooked and attributed to the underlying clinical state.

The importance of potassium in the correct functioning of the isolated heart is well known and easily demonstrated. Deficiency of body potassium has produced necrosis of heart muscle in experimental muscle preparations. The following cardiac effects during hypopotassemia have been noted:¹⁷⁻¹⁹ dilatation of the heart, development of systolic murmurs, ectopic rhythms and profound electrocardiographic changes of a type associated with severe grades of myocardial abnormalities. In addition the blood pressure is usually low. Such profound effects on the heart obviously add to the severity of the clinical picture. These alterations are usually promptly reversed by administration of potassium.

Since a deficiency of potassium affects many vital functions and since the potassium is depleted in intestinal obstruction, it seems very probable that some of the symptomatology of intestinal obstruction may be the result of a deficiency of potassium. This is based on the following: (1) the marked depletion of this important electrolyte in a relatively short period of time following vomiting; (2) the presence of asthenia, weakness, low blood pressure and

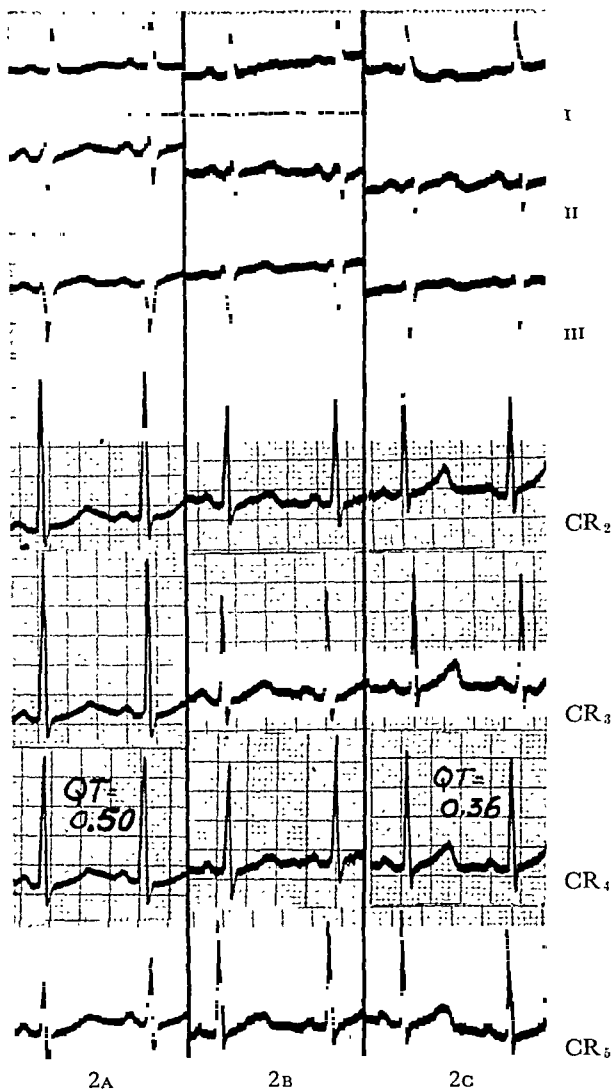


FIG. 2. Case 10. Diagnosis: pyloric obstruction with cyst of pancreas. A, control, K 2.7 mEq./L. Note the low amplitude of the T waves in the precordial leads with lengthening of the Q-T interval to 0.50 second. B, forty-five minutes after 150 cc. of 1.12 per cent potassium chloride had been given. Note diminution of the RST segment depression with a slight increase in the amplitude of the T waves. C, two hours after 300 cc. of potassium chloride had been given. Note the further increase in the amplitude of the T wave. The Q-T interval now measures 0.236 second. The serum potassium at this time was 4.3 mEq./L.

a shock-like state which in many aspects resembles the syndrome of hypopotassemia; (3) the profound electrocardiographic changes; (4) finally administration of potassium results in improvement of the symptoms and signs with almost immediate restoration of the electrocardiogram to normal.

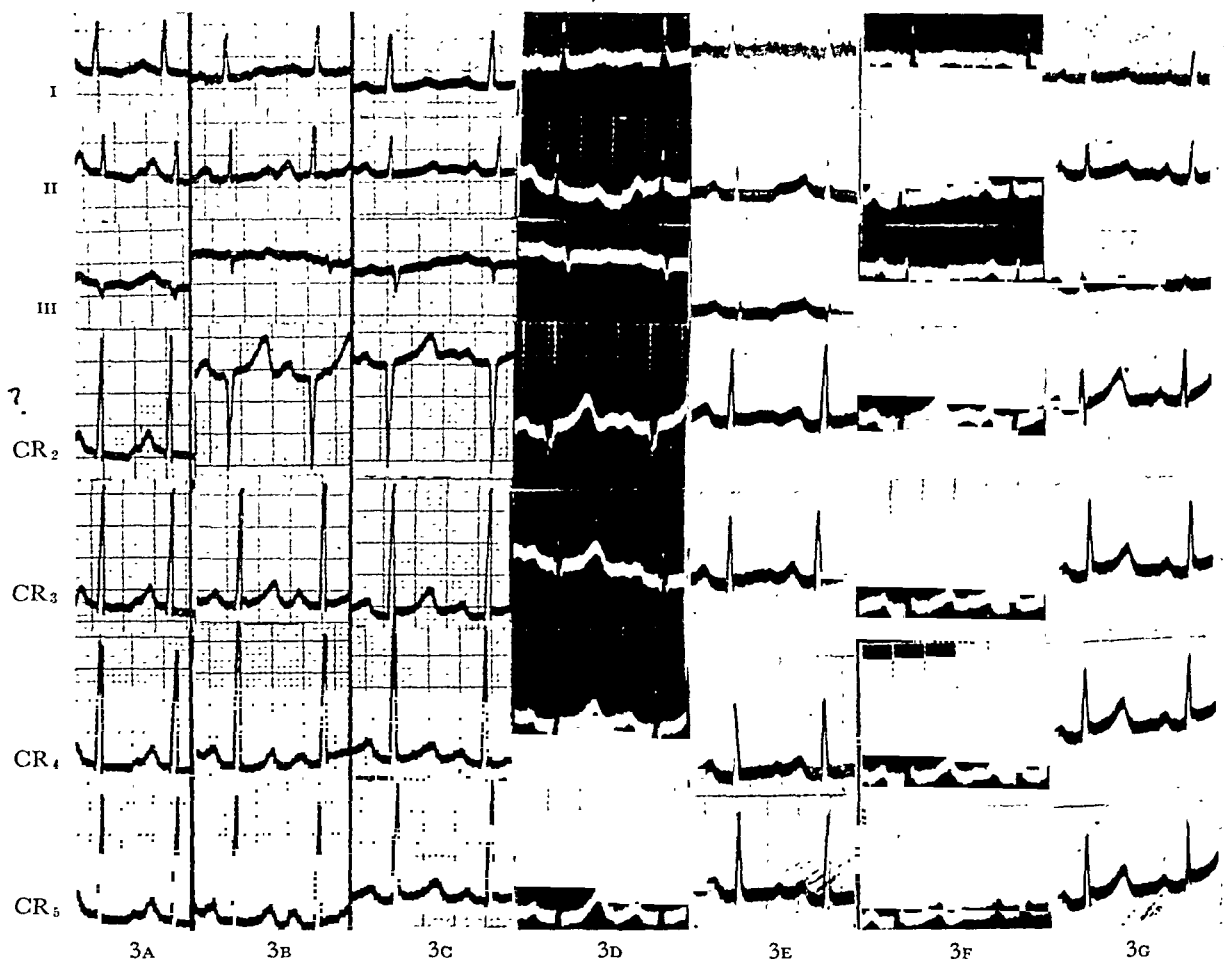


FIG. 3. Case 14, a patient aged eighty-seven. Diagnosis: lower intestinal obstruction due to carcinoma of the sigmoid. A, control, February 2, 1948. Potassium 3.8 mEq./L. Note inverted T waves in all leads with lengthening of the Q-T interval. B, after 150 cc. of potassium chloride had been given in forty-five minutes. The T wave is now upright. C, after 300 cc. had been given in two hours. Note the upright T waves. D, two hours after the potassium had been stopped the electrocardiogram shows no significant change. E, 3.24 hours later it shows flattened T waves in the precordial leads. F, after patient began to take food by mouth it shows a return of the serum potassium to normal with a more upright configuration of the T wave. G, February 7, 1948. shows continuing improvement with a practically normal electrocardiogram.

MECHANISM OF POTASSIUM LOSS THROUGH THE VOMITING PRODUCED BY INTESTINAL OBSTRUCTION

Potassium is lost in intestinal obstruction mainly through direct loss of the electrolyte which is present in the stomach and intestinal secretions. Long-continued vomiting of stomach secretions results in a loss of intra- and extracellular fluids which contain potassium and in the loss of potassium contained in the gastrointestinal secretions. Falconer^{8a,d} observed that the vomitus contained five times the concentration of potassium present in the serum. Frenkel¹⁷ found the potassium in vomitus to be

from 40 to 50 mg. per cent. Austin and Gamman²⁰ observed that gastric juice contains two and one-half times as much potassium as is found in blood serum. With loss of gastric secretions containing free hydrochloric acid, more chloride is lost than sodium, with resulting production of alkalosis. The excess of sodium in proportion to chloride in such states may go into the cell, displacing potassium which is eliminated.

Loss of potassium may also result through procedures designed to treat the vomiting and certain other symptoms caused by intestinal obstruction. Suction by the Wan-

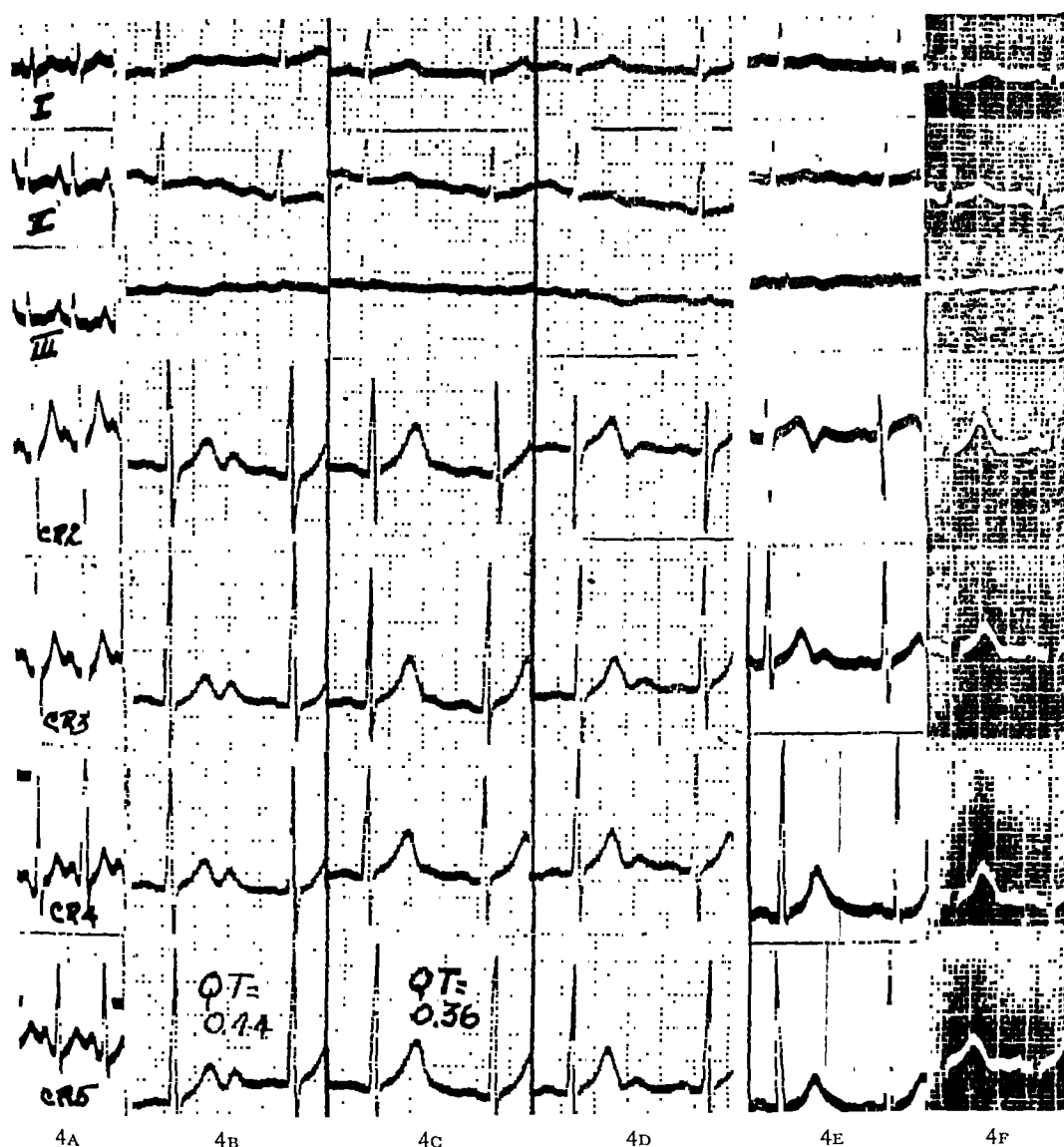


FIG. 4. Illustration of how parenteral fluids which contain no potassium help to produce and maintain low serum potassium levels. Case 15, a patient aged twenty-five. Diagnosis: ruptured duodenal ulcer; the patient vomited only one day prior to admission. A, January 30, 1948, prior to operation. Note tachycardia, upright T waves with slight depression of the S-T segments. Operation was performed (gastro-enterostomy). This patient was given fluids parenterally, saline and glucose, but was unable to take any food by mouth. B, February 6, 1948, control shows T waves to precordial leads of somewhat diminished amplitude followed by a second wave which resembles a U wave but may be part of a T wave (TU wave). The exact end of the T wave is difficult to determine. C, one hour and forty-five minutes after B, after 500 cc. of 1.2 per cent potassium chloride had been given; note increased amplitude of the T wave with absence of the U component of the TU wave. D, one hour later. Notice diminution in amplitude of the T wave with a small U wave. E, February 7, 1948, the patient had begun to take food by mouth earlier on this day. Note potassium to be 2.7 mEq./L. Note diminution of the U wave. F, February 10, 1948, the patient had been eating. The electrocardiogram is now relatively normal.

gensteen or Miller-Abbott tube results in the loss of large amounts of fluid which contain considerable amounts of potassium.

During periods of inanition there is a considerable loss of nitrogen from the cells. This also results in a loss of potassium

which is present in the cells in a ratio of 2 Gm. of nitrogen to 1 mM. of potassium.

Parenteral administration of glucose tends to diminish the serum potassium, causing potassium to enter the cells of the muscles and liver in association with glycogen

formation. This is particularly apt to occur when the cellular potassium is low. In addition glucose tends to produce a transient depletion of salt and helps to eliminate potassium by production of diuresis. On the other hand, glucose has a sparing effect on protein loss which occurs when the patient is not taking food by mouth.

✓ POTASSIUM AND CARDIAC FUNCTION

The action of potassium on the heart is a dual one, this ion affecting both impulse conduction and muscle contractility. The potassium ion is necessary for normal cardiac function; in the absence of potassium the isolated perfused mammalian heart will stop beating in systole. This can be corrected by adding potassium salts. On the other hand, if the concentration of potassium in the perfusion fluid is too high the heart will once again fail, this time in diastole due to a direct depressant action of the ion on the myocardium. Winkler, Hoff and Smith (1938)²¹ administered potassium chloride to dogs by slow intravenous infusion and correlated changes in the electrocardiogram with the serum concentration of potassium. They found that alterations in the T wave appeared at serum concentrations of 5 to 7 mEq./L., depression of the S-T segment at 8 to 10 mEq./L., intraventricular block at 10 mEq./L., disappearance of P waves at 9 to 11 mEq./L. and cardiac arrest at 14 to 16 mEq./L.

The electrocardiogram serves as a fairly good criterion of serum potassium values. This is suggested by the following points: (1) The importance of potassium in muscle contraction, the electrical events of which are recorded by the electrocardiogram; (2) the fact that the heart is the first organ to be affected by this drug following intravenous injection (even before skeletal muscle); (3) the almost immediate alterations in the electrocardiogram upon administration of small doses of potassium (as low as 50 cc. of isotonic potassium chloride); (4) the ability to follow the entire gamut of serum concentrations by the electrocardio-

gram from low to normal, high and toxic concentrations; (5) the failure to encounter typical electrocardiographic patterns of high or low potassium values in normal electrocardiograms.

THERAPEUTIC IMPLICATIONS

These findings indicate that potassium salts should be included in the parenteral fluids used in states associated with excessive vomiting. Darrow²² suggests that the solution used to replace the electrolyte deficit should contain sodium chloride, sodium bicarbonate and potassium chloride when acidosis is present. In alkalosis, on the other hand, a solution containing sodium chloride and potassium chloride is indicated. The importance of establishing and maintaining a normal electrolyte balance cannot be over emphasized. Potassium chloride may be given intravenously, by clysis and by mouth. The intravenous route can be used in patients who are in some degree of shock and in the presence of diabetic acidosis. In other instances intravenous injection is usually associated with more or less severe pain at the injection site which renders its administration difficult. Administration by clysis is usually associated with no discomfort. Administration by mouth can be resorted to when feasible.

TOXICITY OF POTASSIUM

A discussion of the toxic effects of potassium is of importance because the therapeutic indications are to supply potassium in larger quantities to overcome the potassium deficit. Potassium chloride has been given by mouth in doses from 5 to 15 Gm. with no untoward effects to patients with normal renal function. Most of the potassium is eliminated in a period of three to four hours. The toxicity following parenteral injection depends upon the rapidity and amount injected, the potassium level prior to injection, the renal function and probably the condition of the heart at the time of injection. In man, in absence of potassium deficit, the maximum amount considered safe to inject intravenously at one dose is

only 3 to 4 mg./Kg. of body weight.^{11,23} The chief danger in the use of potassium salts is the production of heart block. This develops when the extracellular concentration rises to a little more than twice the normal value. If renal function is good, potassium is rapidly excreted when the concentration in the serum rises. However, rapid intravenous administration can exceed the rate of excretion. Darrow²² estimated that 3.5 mM. of potassium or 0.26 Gm. of potassium chloride per Kg. is a safe dose if used with proper precautions. The total dose should not be given in less than four hours and preferably should be given by slow drip in eight or more hours. For parenteral administration he suggests administration by hypodermoclysis since this method is safer than the intravenous route. Administration of potassium chloride should be combined with sodium chloride or sodium chloride and sodium bicarbonate together with intravenous glucose in water sufficient to supply the water requirement. The glucose probably facilitates the transfer of potassium to the cells.

In the patients of our group, all of whom had low levels of serum potassium and probably low cellular potassium, we injected quantities from 100 to 700 cc. of 1.14 per cent solution without untoward effect in a period of one to three hours. Our experience would tend to indicate that patients in a depleted state of potassium can tolerate large quantities without untoward effects. In case of doubt it is suggested that the injections be given slowly and frequent electrocardiographic checks be made before additional quantities are administered. It is believed that the dangers of potassium intoxication have been considerably overrated.

SUMMARY

1. The effect of severe vomiting upon the serum potassium level is discussed. The serum potassium was found to be low in fifteen patients with protracted vomiting and decreased still further following therapy with saline and glucose solutions. That the

depletion involved not only the serum potassium but the intracellular potassium is suggested by the small rise in serum concentration following injection of relatively large doses of potassium chloride. The relationship of a low serum potassium to serum concentrations of other electrolytes is discussed.

2. The electrocardiographic patterns in hypopotassemia are described and the effects of administration of potassium are noted. The electrocardiogram is a fairly good criterion of potassium deficiency and of considerable importance in the diagnosis of this condition.

3. Administration of potassium resulted in clinical improvement in the patients described and in a return of the electrocardiogram to normal. Administration of this electrolyte in such states is important and in some patients may be life-saving.

Acknowledgments: The authors wish to thank Miss Claire Grobman and Miss Anne D. Arrison for their technical assistance.

REFERENCES

1. BUTLER, A. M., McKHANN, C. F. and GAMBLE, J. L. Intracellular fluid loss in diarrheal disease. *J. Pediat.*, 111: 84, 1933.
2. FENN, W. O. The role of potassium in physiologic processes. *Physiol. Rev.*, 20: 377, 1940.
3. DARROW, D. C. Body-fluid physiology: the relation of tissue composition to problems of water and electrolyte balance. *New England J. Med.*, 233: 91, 1945.
4. DARROW, D. C. Changes in muscle composition in alkalosis. *J. Clin. Investigation*, 25: 324, 1946.
5. TALBOTT, J. H. and SCHWAB, R. S. Recent advances in biochemistry and therapeutics of potassium salts. *New England J. Med.*, 222: 585, 1940.
6. GAMBLE, J. J. Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. Cambridge, 1927. Harvard University Press.
7. SCUDDER, J., ZWEMER, R. L. and WHIPPLE, A. O. Acute intestinal obstruction: evaluation of results in twenty-one hundred fifty cases; with detailed studies of twenty-five showing potassium as a toxic factor. *Ann. Surg.*, 107: 161, 1938.
- ✓ 8a. FALCONER, M. A., OSTERBERG, A. E. and BARGEN, J. A. The serum bases during intestinal obstruction. *Proc. Staff Meet., Mayo Clin.*, 14: 22, 1939.
- 8b. FALCONER, M. A., MURRAY, A., OSTERBERG, A. E. and BARGEN, J. A. Intestinal obstruction in man: alterations in the serum bases and their significance. *Arch. Surg.*, 38: 869, 1939.
- 9a. LANGENDORF, R. and PIRANI, C. L. The heart in uremia. *Am. Heart J.*, 33: 282, 1947.

- 9b. HOFF, H. E., SMITH, P. K. and WINKLER, A. W. The cause of death in experimental uremia. *J. Clin. Investigation*, 20: 607, 1941.
- 9c. KEITH, N. M., BURCHELL, H. B. and BAGGENSTOSS, A. H. Electrocardiographic changes in uremia associated with a high concentration of serum potassium. Report of three cases. *Am. Heart J.*, 27: 817, 1944.
- 9d. WINKLER, A. W., HOFF, H. E. and SMITH, P. K. Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride. *Am. J. Physiol.*, 124: 478, 1938.
- 9e. FINCH, C. A., SAWYER, C. G. and FLYNN, J. M. Clinical syndrome of potassium intoxication. *Am. J. Med.*, 1: 337, 1946.
- ✓ 10. BELLET, S. and DYER, W. W. The electrocardiogram during and after emergence from diabetic coma. *Am. Heart J.*, 13: 72, 1937.
11. SEMLER, R. Über die Beeinflussung der diabetischen Hyperglycämie durch Kalium. *Klin. Wchnschr.*, 4: 697, 1925.
- ✓ 12. HOLLER, J. W. Potassium deficiency occurring during the treatment of diabetic acidosis. *J. A. M. A.*, 131: 1186, 1946.
- ✓ 13. MARTIN, H. E. and WERTMAN, M. Electrolyte changes and the electrocardiogram in diabetic acidosis. *Am. Heart J.*, 34: 646, 1947.
- ✓ 14. NADLER, C. S., BELLET, S. and LANNING, M. The influence of the serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. *Am. J. Med.*, 5: 838, 1948.
15. LANNING, M. The use of the flame photometer in clinical studies (to be published).
- ✓ 16. HUANG, KEH-WEI and MAO YING-CHI. Pa-pin (transient paralysis) complicating Asiatic cholera. *Am. J. M. Sc.*, 214: 153, 1947.
- ✓ 17. FRENKEL, M., GROEN, J. and WILLEBRANDS, A. F. Low serum potassium level during recovery from diabetic coma. *Arch. Int. Med.*, 80: 728, 1947.
18. TALBOTT, J. H. Periodic paralysis. *Medicine*, 20: 85, 1941.
19. GASS, H., CHERKASKY, M. and SAVITSKY, N. Potassium and periodic paralysis. A metabolic study and physiological considerations. 27: 105, 1948.
- ✓ 20. AUSTIN, J. H. and GAMMAN, G. D. Gastric secretion after histamine: sodium and potassium estimation. *J. Clin. Investigation*, 10: 287, 1931.
21. WINKLER, A. W., HOFF, H. E. and SMITH, P. K. Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride. *Am. J. Physiol.*, 124: 478, 1938.
22. DARROW, D. C. Disturbances in electrolyte metabolism in man and their management. *Bull. New York Acad. Med.*, 24: 147, 1948.
23. LASNITZKI, A. and LASNITZKI, M. Comparison of mineral and biologic potassium in diet experiments. *Nature*, 138: 800, 1936.

Hemodynamic Studies in Two Cases of Wolff-Parkinson-White Syndrome with Paroxysmal AV Nodal Tachycardia*

M. IRENÉ FERRER, M.D., RÉJANE M. HARVEY, M.D., HERBERT M. WEINER, M.D.,
RICHARD T. CATHCART, M.D., and ANDRÉ COURNAND, M.D.

New York, New York

SINCE the original description of Wolff-Parkinson-White syndrome,¹ a number of theories have been suggested to explain the abnormal electrocardiographic pattern and associated attacks of paroxysmal tachycardia. The concept of an accessory pathway similar to the bundle of Kent² represents the most acceptable explanation to date. The demonstration of the existence of such an anatomic atrio-ventricular connection in a patient known to present the characteristic clinical and electrocardiographic findings during life offers further evidence of the validity of the concept.³ Pre-excitation of one ventricle with the typical Wolff-Parkinson-White electrocardiographic tracings has been produced experimentally previously;^{4a,b} in addition, using the same pathway, supra-ventricular tachycardia was produced when conduction was retrograde from ventricle to auricle. This evidence provides a satisfactory explanation for many of the features of the anomalous conduction in this syndrome and suggests that the configuration of the QRS complex during the anomalous AV conduction could be explained by fusion from pre-excitation or by early excitation of one ventricle via the anomalous AV pathway and normal depolarization of the other ventricle by means of the normal conduction bundle and Purkinje system.

The theory of pre-excitation suggests the presence of ventricular asynchronism with the lag in ventricular contraction on the side opposite to the anomalous AV bundle. It has been shown⁵ that the electrocardiographic pattern in Wolff-Parkinson-White syndrome may simulate both right and left bundle branch block, indicating an anomalous AV conduction pathway on the left or right side of the heart, respectively.

The manner in which the ventricle on the normal side is depolarized, however, is still uncertain. Originally it was believed that in most instances of Wolff-Parkinson-White syndrome excitation took place via the normal conduction pathway (His bundle and Purkinje system). Depolarization of this type would produce ventricular asynchronism characterized by a normal electrical-mechanical event relationship in the normal ventricle and an early onset of the mechanical event in the ventricle excited via the short-circuit pathway. In Kossman and Goldberger's patient⁶ the anomalous pathway was probably located on the right side as evidenced by a left bundle branch block pattern. However, they found a considerable delay in onset of ejection into the carotid artery which suggests delayed left ventricular contraction. This would be unexpected if activation of the left ventricle occurred via the His bundle and Purkinje system. They believe,

* From the Cardio-Pulmonary Laboratory, Chest Service and the First Medical Service, Columbia University Division, Bellevue Hospital, New York, and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y. Under grants from the Commonwealth Fund and the Life Insurance Medical Research Fund Gift for Study of Action of Certain Cardiovascular Drugs.

therefore, that the delay in contraction is dependent upon abnormal spread of activation through the left ventricular muscle mass and suggest the following sequence of electrical events: ventricular excitation occurred very early on the anomalous side and the excitation wave spread through the right ventricular muscle mass, across the I.V. septum to activate the left ventricular muscle mass before the excitation wave from the AV node traveling over normal specialized conduction pathways reached the left ventricular musculature.

The manner and sequence of ventricular activation may be further clarified by simultaneous registration of the electrical and mechanical events on both sides of the heart. Catheterization of the right ventricular chamber now makes this possible.

Although an abnormal AV pathway is present, it has been constantly stressed that the characteristics of this syndrome are found predominantly in adults without evidence of heart disease. Detailed investigation of the hemodynamics of the circulation in these patients would be of interest to rule out any subclinical cardiac abnormalities. In addition, little precise information is available concerning adaptation of the circulation in man to paroxysmal arrhythmias.

The present study consists in hemodynamic measurements made in two patients with all the characteristic features of the Wolff-Parkinson-White syndrome. Data concerning one of them has been discussed briefly in a previous publication.⁷

METHOD

Using the right heart catheterization technic, intracardiac, peripheral arterial and peripheral venous pressure tracings were recorded by means of Hamilton manometers and were registered simultaneously with the electrocardiogram in two patients with Wolff-Parkinson-White syndrome. A Cambridge instrument of the string galvanometer type was used for inscription of the electrocardiogram. The time lag in mechanical transmission of an impulse through the catheter has been found to be 0.01 second.⁸ Cardiac output, using the direct Fick

principle, was also measured and peripheral vascular resistance and stroke volume were computed. These data were obtained during the anomalous atrioventricular conduction and also during an attack of supraventricular tachycardia in each of the two subjects. One patient (G. F.), a woman of twenty-nine, had no evidence of organic heart or pulmonary disease. The other (K. N.), a male of forty-one, had pulmonary tuberculosis, a left thoracoplasty and some disturbance in pulmonary function. Both were subject to spontaneous attacks of tachycardia. In one patient (G. F.) exploration of the right heart chambers, using a direct intracardiac lead placed in one side of a double lumen catheter,* permitted the electrocardiographic registration of intracavitary potentials simultaneously with the intracardiac pressure curves. The central terminal of Wilson was used as the indifferent electrode in this instance.

ELECTROCARDIOGRAPHIC DATA

The electrocardiograms taken before catheterization in both cases show the short PR and prolonged QRS intervals characteristic of the syndrome. In one patient (G. F.) a series of unipolar precordial leads, using Wilson's central terminal, and the three augmented unipolar limb leads were taken and show a pattern similar to left bundle branch block with delayed activation over the left side of the heart, suggesting a right bundle of Kent. In the second patient (K. N.) the QRS complexes in the standard leads are similar to the right bundle branch block pattern, indicating a left Kent bundle.

Introduction of the venous catheter into the right auricle in each case was followed by production of a paroxysmal supraventricular tachycardia with a ventricular rate of 187 and 178, respectively. Identification of the location of the ectopic pacemaker was difficult in one patient (G. F.) until the registration of the intracardiac (intra-auricular) pattern identified it as AV nodal in origin, with a retrograde P wave falling after the descending limb of the R

* This catheter was supplied by the United States Catheter & Instrument Corp., Glens Falls, N. Y.

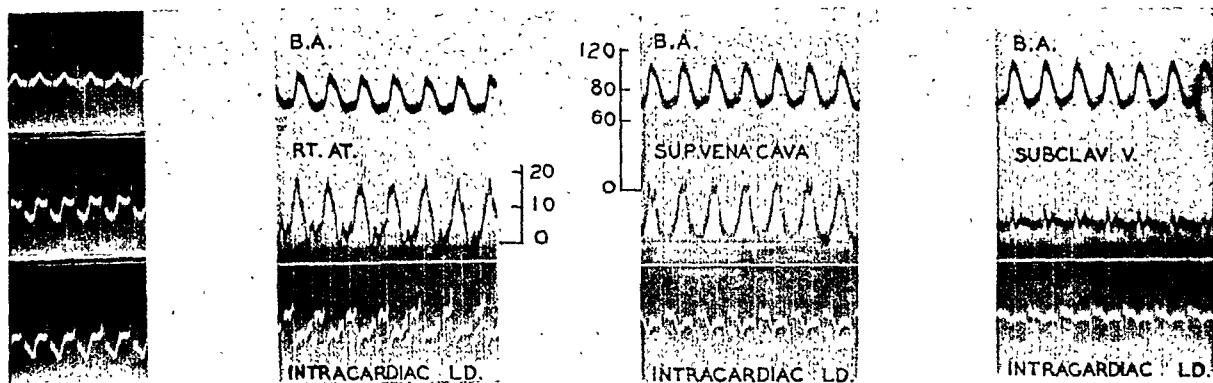


FIG. 1. Records taken during nodal tachycardia in patient G. F. Simultaneous records are shown of the brachial artery (B. A.) pressure and the intracardiac lead with the right atrial, superior vena cava and subclavian vein pressure tracings. The standard leads I, II and III of the electrocardiogram are also shown. Note the markedly abnormal pressure tracings in the right atrium (RT. AT.) and superior vena cava (SUP. VENA CAVA) and the changing character of the intracardiac lead as it was displaced from auricle to subclavian vein. The retrograde P wave (P) is well seen in the auriculogram.

wave. (Fig. 1.) In addition the auricular pressure curves, to be discussed later, proved to be characteristic of this particular arrhythmia as shown by Lewis.⁹ In the second patient (K. N.) no intracardiac lead was available but auricular pressure curves obtained during the supraventricular tachycardia were identical with those of the first patient. This fact plus the electrocardiographic evidence in the standard leads makes the diagnosis of AV nodal tachycardia in this case most likely.

HEMODYNAMIC DATA

Data obtained in the two patients are tabulated in Table 1. For comparison average values obtained in normal subjects are also presented.

During Nodal Tachycardia. In both cases during nodal tachycardia the changes in hemodynamics followed the same pattern. This tachycardia was characterized by a retrograde P wave identified by the intracardiac lead. (Fig. 1.) There was, however, a marked alteration of pressures in the right auricle, superior vena cava and, to a lesser degree, in the subclavian vein (Fig. 1 and Table 1) as compared with the normal tracings. (Fig. 2 and Table 1.) The contour of the abnormal pressure curves in the auricle during nodal tachycardia are identical to those in the jugular tracings described by Lewis⁹ who considered them to be combination A and c waves. The curves in

the superior vena cava resemble those in the right auricle very closely. Jugular vein tracings would, no doubt, approximate those in the superior vena cava since there is no valve between these two venous channels. There is a striking difference, however, in the tracings taken in the subclavian vein, largely because a competent venous valve separates this vein from the innominate. This is evidenced also by the large pressure difference between the superior vena cava and subclavian vein. In spite of the dampening effect of this valve on the pulse wave as it travels through the large intrathoracic veins, a sharp rise in pressure appears corresponding to the rise in pressure in the right auricle. Comparison of the mean pressures in the right auricle during Wolff-Parkinson-White conduction and nodal tachycardia (Table 1) demonstrates the considerable increase in pressure during tachycardia. During aberrant conduction the right atrial mean pressure was 2.0 mm. Hg (27 mm. of water) and during nodal tachycardia the mean pressure rose to 8.0 mm. Hg (109 mm. of water). The peaks of pressure rise actually reach 20 mm. Hg (272 mm. of water) while normal auricular systole rarely exceeds 5 mm. Hg (68 mm. of water). This peak pressure rise approaches the normal right ventricular systolic pressure level. (Table 1 and Fig. 1.)

Onset of the auricular pressure rise during tachycardia occurs 0.11 second after

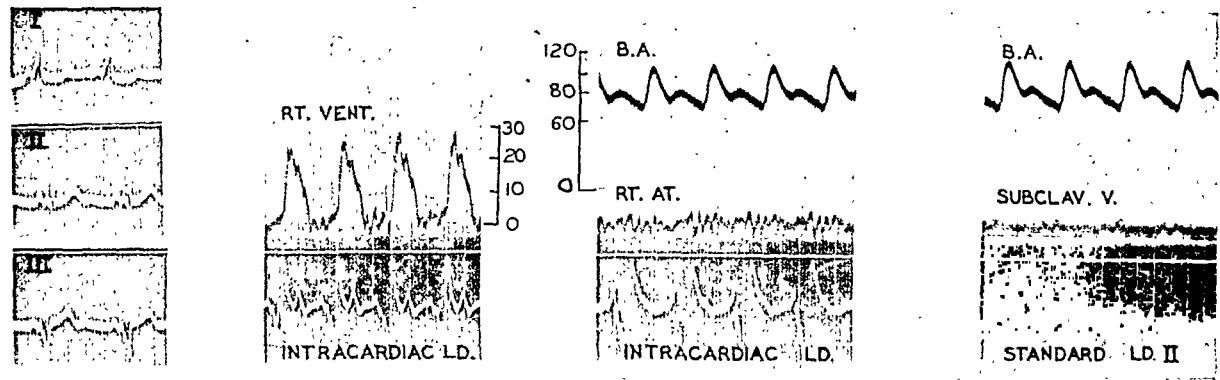


FIG. 2. Records taken during Wolff-Parkinson-White conduction in patient G. F. The blood pressure records were taken in the right ventricle (RT. VENT.), the brachial artery (B.A.), the right atrium (RT. AT.) and the subclavian vein (SUBCLAV. V.). Many artefacts are seen in the tracings from the right ventricle and atrium; the pressures, however, appear essentially normal.

the beginning of the QRS complex and precedes in time the electrocardiographic inscription of the retrograde P wave which falls after the descending limb of the QRS complex. (Fig. 1.) Normally the onset of ventricular systole, as recorded in the auric-

pressure rise in the right auricle is probably due to the summation of two events: (1) regurgitation of blood through the tricuspid valve during ventricular isometric contraction and early ejection and (2) auricular systolic contraction following the

TABLE I
HEMODYNAMIC STUDIES IN TWO PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME
AND NODAL TACHYCARDIA

Patient	Pulse Rate	Blood Pressures in mm. Hg						Cardiac Output		Peripheral Resistance Dynes cm. ⁻⁵ sec.
		Brachial Artery		Right Ventricle (Syst./ Diast.)	Right Atrium (Mean)	Superior Vena Cava (Mean)	Subclavian Vein (Mean)	L./min./m ²	Per Beat	
		(Syst./ Diast.)	(Mean)							
Normal.....	...	120/70	90	28/2	1	1	4	3.12 ± 0.4	50-90	1500
G. F.										
Nodal tachycardia...	187	102/73	80	8	7	5	3.39	27	1130
W-P-W conduction with right bundle of Kent.....	78	104/66	77	28/3	2	..	3	3.16	60	1240
K. N.										
Nodal tachycardia...	178	105/77	90	6	2.30	24	1600
W-P-W conduction with left bundle of Kent.....	121	104/72	84	32/1	1	-1	-1	2.29	34	1590

ular pressure tracing, occurs 0.06 to 0.09 second after the beginning of the QRS. The abnormally high upward deflection in the auricular pressure wave simulates a ventricular pressure curve and has lost the normal A, C and V waves. This abnormal

retrograde P wave. Both events occurring in rapid succession would be inscribed as a single upward deflection of marked amplitude. The cause of the tricuspid regurgitation is probably to be ascribed to the absence of a normal auricular systole

occurring near the end of ventricular diastole. The role played by auricular systole in the closure of the AV valves has been emphasized by many authors. According to Wiggers,¹⁰ production of turbulent flow with formation of eddies tends to close the valves. In addition an area of negative pressure develops in the axial stream when the jet of blood is suddenly stopped at the end of auricular systole. Into this area of negative pressure blood is drawn from the sides "much as water in the wake of a ship" and the valves are carried with the blood and approximate their leaflets.

As in nodal tachycardia the auricular systole follows the onset of ventricular systole, these mechanisms for the valve leaflet approximation are not operating at the proper time in relation to ventricular systole. Furthermore, mechanical auricular systole occurs against a closed tricuspid valve since the ventricle is contracting and intraventricular pressure is high. The very high peak of auricular pressure probably favors retrograde flow into the intrathoracic venous system as far as the peripheral venous valves during part of the cardiac cycle. Thus auricular filling which normally takes place during ventricular systole is inadequate because of retrograde flow and abnormally high auricular pressures. The filling of the auricles is therefore limited to the very short interval during which the auricular pressure is falling and the filling of the right ventricle during the short period of diastolic inflow is probably inadequate.

It is not surprising, therefore, that the cardiac output during tachycardia remains unchanged as compared to the cardiac output during Wolff-Parkinson-White conduction and normal rhythm and that stroke volume is considerably reduced. It should be emphasized that the cardiac output was determined fifty minutes after the onset of nodal tachycardia and it is impossible to predict how long the systemic flow would remain at that level.

It has been just noted that the mean pressure in the subclavian vein is lower

than in the large veins of the thorax, a situation somewhat different from that arising in the usual type of tricuspid insufficiency¹¹ with right ventricular and auricular dilatation associated with large blood volumes and cardiac failure. The peripheral venous flow in the arm must therefore be discontinuous, taking place only after the large retrograde wave moving from the auricle into the large vessels of the thorax has passed. As is well known clinical observation of jugular venous pulsations provides in these arrhythmias more information than measurement of the peripheral venous pressure.

In an attempt to secure right ventricular pressure tracings during nodal tachycardia in both cases the catheter was advanced from the right auricle into the right ventricle. This maneuver broke the nodal tachycardia in both patients. In one (G. F.), a continuous electrocardiogram was recorded during movement of the catheter and resumption of normal sinus rhythm with Wolff-Parkinson-White conduction was preceded by a premature ventricular systole.

During Wolff-Parkinson-White Conduction. During normal sinus rhythm with Wolff-Parkinson-White conduction the hemodynamics of the circulation in one patient (G. F.) were entirely normal. The cardiac output, peripheral vascular resistance and arterial blood pressures were the same as during tachycardia (Table 1) but right auricular and subclavian vein mean pressures were lower. The right ventricular pressures were within normal limits. (Table 1 and Fig. 2.)

The second patient (K. N.) had a low cardiac output and a slightly elevated right ventricular systolic pressure during sinus rhythm with Wolff-Parkinson-White conduction. (Table 1.) These findings are compatible with the diagnosis of early cor pulmonale related to chronic pulmonary disease and collapse of one lung by thoracoplasty. Arterial blood pressures and peripheral vascular resistance were normal and the same as when measured during nodal tachycardia. The right ventricular

diastolic and right auricular mean pressures were within normal limits and the latter was considerably lower than during the arrhythmia. Stroke volume increased but was still low during aberrant conduction. This resulted from the dual effect of low

mechanical relationship seen in these two patients (Table II) during aberrant AV excitation and nodal tachycardia, comparison with normal intervals (Table II) is essential. Three time intervals are to be considered: (1) the time interval between the beginning

TABLE II

ELECTROCARDIOGRAPHIC DATA AND ELECTRICAL MECHANICAL INTERVALS IN TWO PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME

Patient	Pulse Rate	Electrocardiographic Data. (sec.)		Electrical Mechanical Intervals, (sec.)		
		PR Interval	QRS Interval	P-AT _s	Q-RV _s	Q-BA _s
Normal.....	60-100	0.12-0.20	0.06-0.10	0.05-0.11	0.06-0.09	0.14-0.19
G. F.						
Nodal tachycardia.....	187	0.06	0.18
W-P-W conduction with right bundle of Kent.....	78	0.08	0.12	0.08	0.10	0.24
K. N.						
Nodal tachycardia.....	178	0.08	0.19
W-P-W conduction with left bundle of Kent.....	121	0.11	0.12	0.06	0.16	0.24

cardiac output and sinus tachycardia. (Table I.)

In summary, a comparison of the hemodynamic data obtained during Wolff-Parkinson-White conduction and during paroxysmal nodal tachycardia in these two patients shows that during the latter: (1) the cardiac output was unchanged with the development of striking pressure abnormalities in the right auricle and despite marked increase in ventricular rate, (2) the stroke volume was greatly diminished and (3) the arterial blood pressure and peripheral vascular resistance were not altered.

ELECTRICAL-MECHANICAL EVENTS

It is generally agreed that there is no abnormality in auricular activation in Wolff-Parkinson-White syndrome. The basic disturbance appears to be abnormal ventricular excitation. An analysis of the time intervals between electrical and mechanical events in the cardiac cycle was undertaken in order further to elucidate this problem. In considering the abnormal electrical-

of the P wave and the onset of auricular systole (P-AT_s), (2) the time interval between the beginning of the initial deflection of the QRS complex (Q) and the onset of right ventricular systole (Q-RV_s) and (3) the time interval between the beginning of Q and the onset of pressure rise in the brachial artery (Q-BA_s). This latter gives indirect information as to the contraction of the left ventricle. No attempt has been made to delineate the relationship in time of diastole to the electrical events.

During Nodal Tachycardia. In both patients during the AV nodal tachycardia it was impossible to determine the P-AT_s time interval because of the distorted pressure curve and the presence of a retrograde P wave. No information is available concerning events in the right ventricle during the arrhythmia since passage of the catheter into this chamber interrupted the tachycardia and restored the aberrant conduction and sinus rhythm. From analysis of the relationship of electrical-mechanical events in the brachial artery (Table II) it can be

seen that the Q-BA_s time during tachycardia was normal in both cases. At this time presumably depolarization of both ventricles was accomplished via the normal conduction system as evidenced by the normal QRS interval (Table II) of 0.06 and 0.08 second, respectively.

During Wolff-Parkinson-White Conduction. During Wolff-Parkinson-White conduction and sinus rhythm the electrical-mechanical event relationship in the right auricle, as expressed by the P-AT_s interval, was normal in both patients.

Analysis of the ventricular events, however, reveals similar abnormalities in both patients. These are characterized by prolongation of both the Q-BA_s and Q-RV_s intervals, indicating a delay in the onset of the systole in both the right and left ventricles. It seems evident that neither ventricle is activated by the normal conduction pathways. Rather it is likely that the ventricular excitation wave is conducted entirely via muscular tissue. Since the velocity of impulse transmission is slower in muscle (approximately 400 mm./sec.) than in specialized conduction tissue (4,000 mm./sec.),⁹ prolongation of the Q-BA_s and Q-RV_s intervals is compatible with the theory that the short circuit pathway carries the impulse directly into ventricular muscle mass, depolarization then spreading through both ventricles by muscular pathways. A necessary corollary to the theory of muscular conduction in both ventricles during anomalous excitation is that the accession wave traveling over the normal conduction system on the contralateral side arrives to find the normal ventricle already partially depolarized and therefore refractory. Marked prematurity of conduction to the ventricle via the anomalous bundle⁶ or relative prolongation of the delay at the AV node of the normal electrical activation,⁵ or both, would permit the pre-excitation wave to reach the I.V. septum and activate the normal side before the arrival of the normally progressing impulse. This would occur provided the terminus of the aberrant AV bundle is not

too far from the interventricular septum. Mahaim¹² has identified and stressed this particular location of an accessory pathway. Consideration of the electrical-mechanical events in each case supports this theory.

In the patient (G. F.) with an electrocardiographic pattern similar to left bundle branch block and suggesting a right bundle of Kent, the onset of systole is markedly delayed on the left or normal side of the heart, as evidenced by a prolonged Q-BA_s time interval (Table II), while the Q-RV_s interval is only slightly prolonged. The marked lengthening of the Q-BA_s time interval and the delayed activation over the left side of the heart in the precordial leads suggest that the impulse reaches the left ventricle only after initial activation of the right.

In the patient (K. N.) who had a right bundle branch block pattern and presumably a left bundle of Kent the onset of systole was markedly delayed in both ventricles as evidenced by prolonged Q-RV_s and Q-BA_s time intervals. (Table II.) The lengthening of these time intervals can be explained by an aberrant AV conduction into the base of the left ventricle with subsequent activation of both ventricles by spread of the impulse through left ventricular muscle mass, interventricular septum and right ventricular muscle mass. However, both patients had identical Q-BA_s time intervals although in one the aberrant bundle was opposite in location to the other. If one assumes that it requires approximately 0.04 to 0.06 second⁶ for an impulse to travel from one ventricle to the other, as is the case in patients with true bundle branch block, then the patient (G. F.) who had a right aberrant bundle may have ventricular asynchronism entirely due to late activation of the lagging left ventricle. In the patient with a left anomalous pathway (K. N.) the delay on the right side is easily explained by the time required for the impulse to reach and to stimulate fully the right ventricle. The delay on the left side, however, is as great as on the right. If it requires 0.05 second to activate com-

pletely the thicker ventricle, even though the impulse reaches it first in this patient, it is difficult to see why the Q-BA_s time in the first patient (G. F.) is not longer since the impulse starts from the right ventricle in this instance and must travel over to the left. It may be that the location of the distal end of the aberrant pathway is sufficiently variable in patients with the bundle of Kent on the same side to account for entirely different sites of origin of the initial ventricular excitation as well as different sequences of depolarization. If in the patient with a right Kent bundle (G. F.) the bundle is long and the terminus lies near the interventricular septum, the excitation wave would spread in opposite directions and depolarization begin at nearly the same time in each ventricle. The difference in delay on each side, therefore, would be largely a matter of ventricular thickness. If the bundle is short and the terminus in the second patient lies near the base of the left ventricle, the pathway taken by the excitation wave would be more circuitous and the delay in the left ventricular mechanical event would be due to slow progression of the wave through a thick wall. Delay on the right would result both from the late arrival of the impulse on that side and delayed progression of electrical stimulation through the thinner right ventricular wall. With a cor pulmonale, the increased right ventricular muscle mass might further prolong the Q-RV_s. The net result in this instance would be a nearly synchronous contraction of both ventricles.

In summary, the data obtained by analysis of electrical-mechanical events in this syndrome suggests that the anomalous bundle is probably located on opposite sides of the heart in each patient. There is probably abnormal activation of both ventricles in each case, due in large measure to exclusive muscular conduction of the excitation wave. Ventricular asynchronism may and probably does exist in one patient and is probably absent in the second patient because of: (1) differences in location of the terminus of the aberrant pathway with resultant alteration of the

sequence of depolarization and (2) differences in thickness of the two ventricles.

INTRACAVITARY POTENTIALS

In one patient (G. F.), using the intracardiac electrode, intracavitary potentials were recorded during nodal tachycardia and sinus rhythm with Wolff-Parkinson-White conduction.

During nodal tachycardia, as can be seen in Figure 1, with the electrode in the auricle the QRS complex probably consists of a small initial positive deflection (R) followed by a deep negative deflection (S) and small final positive wave (R'). Immediately following the QRS complex there is a biphasic rapid deflection characterizing the retrograde P wave. When the intracavitary electrode was located in the superior vena cava the ventricular complex no longer showed an initial positive deflection. The retrograde P wave has almost entirely lost its biphasic character. The pattern recorded in the subclavian vein no longer shows any P wave and the negative T wave is now discernible.

Standard leads in this patient show supraventricular tachycardia. Further identification of the origin of the arrhythmia was made possible only by location of the retrograde P wave in the auriculogram.

During Wolff-Parkinson-White conduction with presumably a right accessory pathway, the intracavitary potentials recorded in the right ventricle in G. F. (Fig. 2) were characterized by an upright P wave and a QRS which begins with a small positive deflection (R) followed by a rapid but small S wave and a large final R'. The T wave is upright and there may be a small U wave which follows it. The auriculogram showed the expected variation of the P wave with different positions of the electrode. When the electrode was near the tricuspid valve (Fig. 2) in about the mid-auricular position, the ventricular deflections consist of a large negative followed by a large positive component. The T wave is difficult to delineate. With the electrode high in the auricle, near the

SA node, the QRS consists of R, S and R' with a positive T wave.

The ventriculogram does not resemble those seen with classical left bundle branch block.^{13,14} There appears to be no current of injury to distort the curve. However, the QRS does not have the usual right ventricular pattern of a small R and a deep S^{13,14} reported as normal. Insufficient knowledge concerning the different patterns that may be found in normal right ventricles precludes further interpretation of the intracavitary potentials in this patient.

SUMMARY AND CONCLUSIONS

Using the right heart catheterization technic, intracardiac and peripheral arterial and venous pressure tracings were recorded simultaneously with the electrocardiogram in two patients with Wolff-Parkinson-White syndrome. Cardiac output, peripheral resistance and stroke volume were also measured. These data were obtained during the anomalous atrioventricular conduction and also during an attack of supraventricular tachycardia in each of the two patients.

In one case exploration of the right heart chambers, using a direct intracardiac lead, permitted the electrocardiographic registration of intracavitary potentials simultaneously with the intracardiac pressure curves. In this case identification of the supraventricular tachycardia as nodal could only be made in the intracardiac lead tracing.

The information obtained in these two patients suggests that the anomalous conduction pathway was located on different sides of the heart in each patient and that ventricular excitation was not normal in either ventricle during aberrant conduction.

Hemodynamic studies during the first fifty minutes of the nodal tachycardia demonstrate that there were marked pressure and presumably filling abnormalities in the right auricle related to tricuspid insufficiency and an auricular systole abnormal in time. With these alterations and despite the increased rate, the cardiac output was unchanged.

During Wolff-Parkinson-White conduction and sinus rhythm, intracardiac and

arterial blood pressures and systemic flow were normal in one patient. Abnormalities in these values found in the other patient could be ascribed to a coincident early cor pulmonale.

REFERENCES

1. WOLFF, L., PARKINSON, J. and WHITE, P. D. Bundle branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia. *Am. Heart J.*, 5: 685, 1930.
2. KENT, A. F. S. Illustrations of the right lateral auriculo-ventricular junction in the heart. *J. Physiol.*, 48: 63, 1914.
3. WOOD, F. C., WOLFERTH, C. C. and GECKELER, G. D. Histological demonstration of accessory muscular connections between auricle and ventricle in a case of short PR interval and prolonged QRS complex. *Am. Heart J.*, 25: 454, 1943.
- 4a. BUTTERWORTH, J. S. The experimental production of the syndrome of apparent bundle branch block with short P-R interval. *J. Clin. Investigation*, 20: 458, 1941.
- 4b. BUTTERWORTH, J. S. and POINDEXTER, C. A. Short P-R interval associated with a prolonged QRS complex. A clinical and experimental study. *Arch. Int. Med.*, 69: 1437, 1942.
5. BURCH, G. E. and KIMBALL, J. LER. Notes on the similarity of QRS complex configurations in the Wolff-Parkinson-White syndrome. *Am. Heart J.*, 32: 560, 1946.
6. KOSSMAN, C. E. and GOLDBERGER, H. E. Sequence of ventricular stimulation and contraction in a case of anomalous atrioventricular excitation. *Am. Heart J.*, 33: 308, 1947.
7. RICHARDS, D. W., JR., COUNNAND, A., MOTLEY, H. L., DRESDALE, D. T. and FERRER, M. I. Relation between electrical and mechanical events of the cardiac cycle in normal and abnormal clinical states. *Tr. A. Am. Physicians*, 9: 65, 1947.
8. COUNNAND, A., MOTLEY, H. L., HIMMELSTEIN, A., DRESDALE, D. and RICHARDS, D. W., JR. Latent period between electrical and pressure pulse waves corresponding to right auricular systole. *Proc. Soc. Exper. Biol. & Med.*, 63: 148, 1946.
9. LEWIS, T. *The Mechanism and Graphic Registration of the Heart Beat*. 3rd ed. London, 1925. Shaw & Sons, Ltd.
10. WIGGERS, C. J. *Physiology in Health and Disease*. Philadelphia, 1944. Lea & Febiger.
11. BLOOMFIELD, R. A., LAUSON, H. D., COUNNAND, A., BREED, E. S. and RICHARDS, D. W., JR. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardiocirculatory disease. *J. Clin. Investigation*, 25: 639, 1946.
12. MAHAIM, I. Kent's fibers and the AV paraspecific conduction through the upper connections of the bundle of His-Tawara. *Am. Heart J.*, 33: 651, 1947.
13. HECHT, H. Potential variations of right auricular and ventricular cavities in man. *Am. Heart J.* 32: 39, 1946.
14. BATTRO, A. and BIDOGGIA, H. Endocardiac electrocardiogram obtained by heart catheterization in the man. *Am. Heart J.*, 33: 604, 1947.

Studies on Coronary Circulation*

V. Quantitative Changes in a Serum Mucoprotein Following the Occurrence of Myocardial Infarction

BENJAMIN SIMKIN, M.D., H. C. BERGMAN, PH.D. and M. PRINZMETAL, M.D.
Los Angeles, California

THE diagnosis of myocardial infarction is not infrequently a difficult one, especially in cases in which the electrocardiographic changes are absent, minimal or atypical. In these situations laboratory procedures such as the sedimentation rate and white count, which are commonly used as diagnostic aids, may be of little value because of the non-specificity of these tests. With these facts in mind, it was postulated that an approach could be made to a more accurate diagnosis of myocardial infarction if substances derived from the breakdown of infarcted heart muscle could be detected and measured in the blood or urine of such patients.

Since the breakdown of infarcted heart muscle by proteolytic enzyme activity could conceivably result in the release of cardiac muscle proteins and their breakdown products into the blood, it was thought that investigation of serum protein changes following myocardial infarction would be of interest. The previous work of Winzler and Burke¹ and the continuing studies of Winzler² on serum proteose changes in animals and man with cancer attracted our attention to study of the quantitative change of this serum component following the occurrence of myocardial infarction. Although this material was originally designated as a proteose because it is heat-stable, perchloric acid soluble, non-dialyzable and can be salted out with saturated ammonium sulfate,³ further studies on the chemical and physical properties of this material by

Winzler² indicate that it may be classified more properly as a mucoprotein. Therefore, this communication constitutes a study of the quantitative changes in a serum mucoprotein following the occurrence of myocardial infarction in man. Although an increase in the serum concentration of this mucoprotein following myocardial infarction cannot be considered specific for this condition, as originally hoped, this procedure has nevertheless proved helpful as a diagnostic aid under certain circumstances.

METHOD AND MATERIALS

Principle. The method for determination of the serum mucoprotein component† studied here was adapted from the procedure recently developed by Winzler and his associates.³ It is based upon the fact that this material is not precipitated by 6 per cent perchloric acid which does, however, precipitate the other serum proteins. Following removal of the serum proteins by perchloric acid, the mucoprotein which has remained in solution is precipitated by phosphotungstic acid, and the precipitate is quantitatively measured by the biuret or tyrosine color reactions. In this study the biuret color reaction was used for determination of serum mucoprotein.

Details of Method. To an exactly measured volume of serum, preferably 6 ml. obtained from 15 to 20 ml. of clotted blood, is added a solution of 6 per cent perchloric acid in an amount which is twice the volume of the serum sample. The mixture is shaken well and allowed

† For the sake of convenience this material will be referred to as "serum mucoprotein" throughout the rest of this paper.

* From the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, Calif. Endowed by grants from the Blanche May and Beaumont Trust Funds.

to stand ten minutes. A heavy whitish-yellow precipitate forms. At the end of ten minutes the solution is filtered, using No. 50, 9.0 cm. Whatman filter paper. The time required for complete filtration varies from forty-five minutes to two hours. The filtrate should be clear and colorless; if any turbidity is seen, it should be refiltered through the same filter until clear. Exactly 10 ml. of the filtrate, measured with a 10 ml. volumetric pipet, is placed in a 15 ml. centrifuge tube and 2 ml. of 5 per cent phosphotungstic acid in 2 N HCl is added. A flocculent precipitate is formed. The solution is gently agitated and allowed to stand for ten minutes. The precipitate is separated by centrifugation for ten minutes. The clear supernatant is decanted and the precipitate is washed with 5 ml. of 5 per cent phosphotungstic acid in 2 N hydrochloric acid. After centrifugation the supernatant is again decanted.

The precipitate is dissolved in exactly 5 ml. of 0.2 N sodium hydroxide. At the same time a blank tube is prepared with 5 ml. of 0.2 N sodium hydroxide and a standard tube with 5 mg. casein in 5 ml. of 0.2 N sodium hydroxide. One ml. biuret reagent* is added to the blank, the standard and the unknown sample. The tubes are placed in the dark for one hour to permit full color development. At the end of an hour the color in the tubes is read with a Klett-Summerson Photoelectric Colorimeter using a green filter No. 54.

The serum concentration of this material may be calculated by the following formula:

$$\text{Mg. mucoprotein per 100 ml. serum} = \frac{\frac{\text{Colorimetric reading of unknown}}{\text{Colorimetric reading of standard}} \times 5 \text{ mg. casein} \times 100}{\frac{\text{Volume of filtrate used for determination}}{\text{Total volume of filtrate}}} \times \text{volume serum}$$

Normal mucoprotein values ranged from 40 to 90 mg. per 100 ml. of serum. These values which were obtained in this laboratory correlated well with those found by Winzler.³

Serial serum mucoprotein determinations were performed on twenty-three patients in whom the diagnosis of a recent myocardial infarction was made and subsequently was confirmed by either electrocardiographic changes

* Composition of biuret reagent: 500 mg. $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, 5 ml. 28 per cent ammonium hydroxide, 85 ml. 40 per cent carbonate-free sodium hydroxide diluted to 100 ml. with distilled water.

or pathologic examination of the heart. The usual procedure was to determine the serum mucoprotein level twice a week for the first two weeks and then once weekly thereafter for the duration of the hospital stay. All patients were hospitalized and practically all of the blood samples were obtained between 9 and 11 A.M. In a few patients serum mucoprotein levels were obtained two to four months after onset of the illness at a time when satisfactory convalescence from the acute episode had been brought about. The corrected Wintrobe sedimentation rate⁴ was obtained each time a mucoprotein determination was made. In a few instances the Linzenmeier sedimentation rate⁵ was taken. Serum mucoprotein levels were correlated with sedimentation rate, leukocyte count, body temperature of the patient and the patient's clinical status. In this series there were eight deaths. Autopsy was performed on two of these patients and in both instances the clinical diagnosis was confirmed.

Serum mucoprotein levels were also determined in a second series of twelve patients who complained of prolonged chest pain and in whom it was at first difficult to tell whether or not a recent myocardial infarction had occurred. There were patients in this group who had angina pectoris, paroxysmal tachycardia, fibrosis and pain of psychogenic origin.

Serum mucoprotein levels were determined in a third group of twenty-six hospital patients with miscellaneous non-cardiac illnesses.

RESULTS

Serum Mucoprotein Changes in Myocardial Infarction. In all but two of the twenty-three patients with a proven diagnosis of myocardial infarction there was a clearcut rise in the serum mucoprotein level. It was found that a characteristic rise and fall of serum mucoprotein occurred following the clinical onset of the disease. (Fig. 1.) The peak of the rise in serum mucoprotein exceeded the value considered as the upper limit of normal in all but three instances. In

this series the actual rise in mucoprotein above each patient's normal value varied from 22 to 160 mg. per 100 ml. A tabulation of the results obtained for each patient may be seen in Table 1.

It was found that serial determinations

first two days. For example, in this series there were mucoprotein levels above the range of normal in five of eight determinations performed on patients during the first two days. The peak of the rise in mucoprotein occurred on the fifth and sixth days.

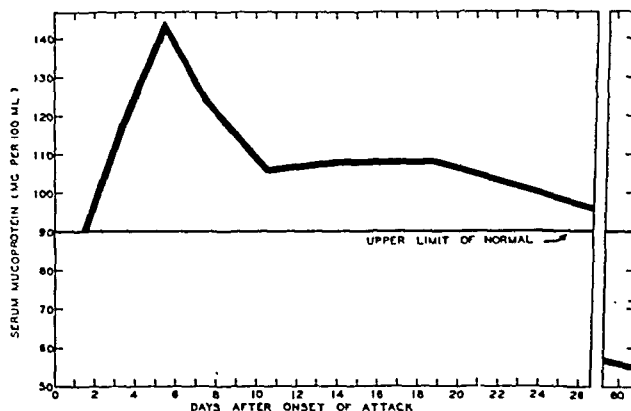


FIG. 1. Curve illustrating serum mucoprotein response following myocardial infarction. This curve is based upon the average serum mucoprotein values of the twenty-three cases listed in Table 1.

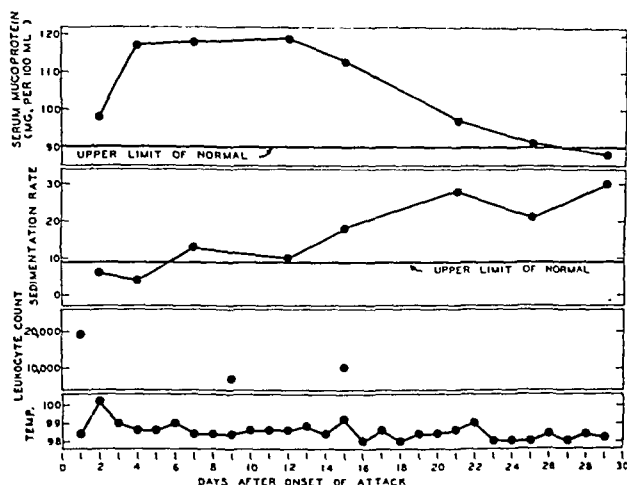


FIG. 2. A typical serum mucoprotein response to myocardial infarction. Case J. R., a sixty-six year old white male. Diagnosis: recent myocardial infarction of the anterior wall. It will be noted that there was no correlation between serum mucoprotein and sedimentation rate (Wintrobe).

of serum mucoprotein offered a great deal more information than the absolute serum mucoprotein level obtained at any specific time after the onset of the patient's attack. A definite elevation of the serum mucoprotein did not take place in all patients until the third day after onset of the attack. In individual cases there may or may not be an increase in this substance during the

On the whole, this elevation was maintained until the ninth day; thereafter the serum mucoprotein concentration gradually declined, approaching normal values at the end of a month. After two or three months the values always returned to the normal range. In individual cases there was a variation in the time at which the mucoprotein level returned to normal. This may

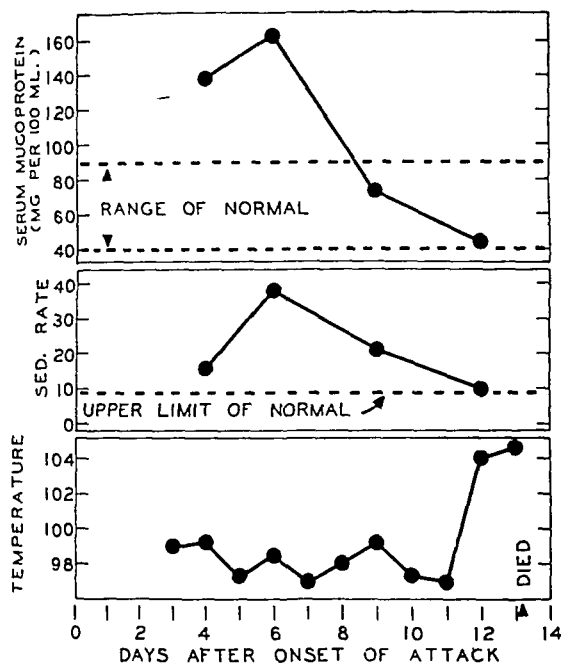


FIG. 3. Serum mucoprotein response to myocardial infarction with terminal azotemia and shock. Case L. M., a fifty-four year old white male. Diagnosis: recent myocardial infarction of posterior wall. The patient died with terminal azotemia and shock on the thirteenth day after coronary occlusion; no autopsy was obtained. A return to normal mucoprotein values occurred despite shock and terminal azotemia. In this case the sedimentation rate (Win-trobe) paralleled the serum mucoprotein values.

occur as early as the tenth day. Typical mucoprotein responses to myocardial infarction as shown in Figures 2, 3 and 4.

The following two cases illustrate the fact that serial mucoprotein determinations were more informative than any single level. In one, Table 1, Case 9, a patient who had bronchogenic carcinoma with bone metastases developed an anterior wall myocardial infarction. The characteristic rise and fall of serum mucoprotein noted after a myocardial infarction was superimposed upon an already elevated mucoprotein level caused by the pre-existent bronchogenic carcinoma. Although a single determination for mucoprotein would have meant little in this case, serial determinations aided in showing the characteristic changes observed following myocardial infarction. In the second case, Table 1, Case 22 (Fig. 5), a patient who had a coronary occlusion some months previously continued to have anginal attacks and was hospitalized because of severe substernal pain of two hours' duration. Serial determinations showed no change in the serum mucoprotein level

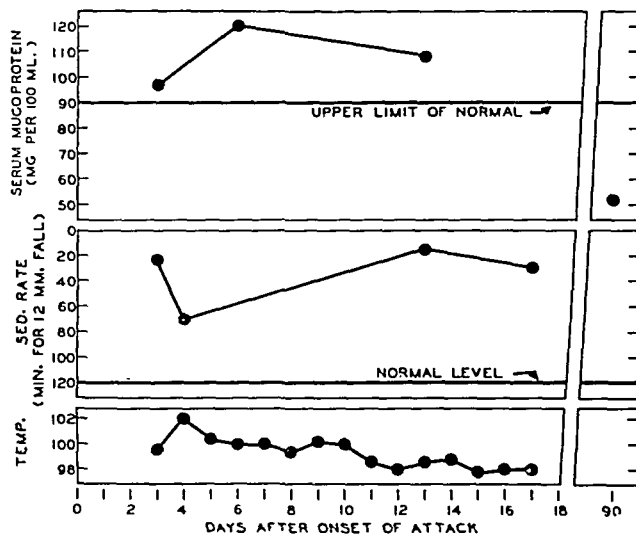


FIG. 4. Graph illustrating optimum times for serial serum mucoprotein determinations. Case I. C., a sixty year old white male. Diagnosis: recent myocardial infarction of posterior wall. In this case the rise in serum mucoprotein during the first week aided in the diagnosis because the electrocardiographic changes were not well defined until the twelfth day. There seemed to be no apparent correlation between sedimentation rate (Linzenmeier) and serum mucoprotein.

which was below the usual range of normal. On the eighth hospital day he had another attack of severe substernal pain with collapse. Following this there was a rise of 22 mg. per 100 ml. in the concentration of serum mucoprotein. Although the highest

patients of this series did not exceed the value established as the upper limit of normal. One of these patients, Table 1, Case 22, was described in the preceding paragraph. Another of these patients, Case 16, died within twenty-four hours after

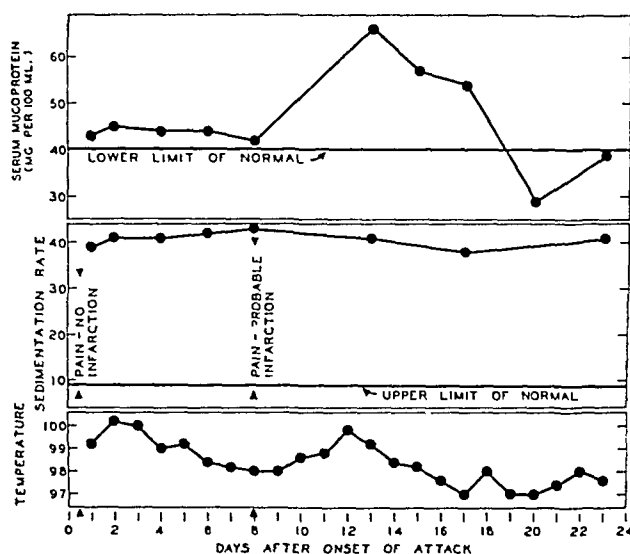


FIG. 5. Graph illustrating the importance of serial serum mucoprotein determinations although values occur within the normal range. Case I. S., a forty-nine year old male. Diagnosis: myocardial infarction. A patient with two previous coronary occlusions had angina pectoris for six months. He was admitted to the hospital with severe substernal pain. Despite fever and rapid sedimentation rate (Wintrobe) the serum mucoprotein remained normal and no electrocardiographic changes were noted. On the eighth hospital day the patient suffered another severe attack of substernal pain associated with collapse. The temperature was elevated, serum mucoprotein rose 22 mg. per 100 ml. above the previous level and changes in the electrocardiographic record were atypical. The second attack was interpreted as myocardial infarction whereas the first episode was considered to be premonitory symptoms anticipating the myocardial infarction.

absolute value of serum mucoprotein obtained was within the range of normal (66 mg. per 100 ml.), the significant increase in mucoprotein concentration, correlated with the characteristic curve of the rise and fall of serum mucoprotein, indicated the occurrence of a myocardial infarction following the second attack of pain. The occurrence of a few atypical ECG changes following the second bout of pain but not following the first strengthened this conclusion.

As just mentioned the highest mucoprotein level obtained in three of the

onset of his attack and the single mucoprotein determination obtained was normal. However, serum mucoprotein may not be increased on the first day. The third patient, Case 10, had an anterior wall myocardial infarction with a typical clinical picture and electrocardiographic changes. In this case the mucoprotein concentration rose only 15 mg. per 100 ml. to a peak value of 93 mg. per 100 ml. Although a rise in serum mucoprotein did occur in this case, the findings were not considered clearcut enough to indicate a positive response to myocardial infarction.

TABLE 1
RELATION OF MYOCARDIAL INFARCTION TO SERUM MUCOPROTEIN

Case	Age	Sex	Diagnosis	Days after Onset of Attack Serum Mucoprotein (mg. per 100 ml.)																														
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	24	25	26	29	40	60	90	120	
1 B	59	M	Old anterior wall infarct; recent posterior wall infarct	300	165	139	178	...	X*
2 K	63	M	Anterior wall infarct	178	84	64
3 S	61	M	Anterior wall infarct	151	122	116
4 S	54	M	Posterior wall infarct	143	148
5 G	57	M	Posterior wall infarct	183	106	51
6 H	33	M	Anterior wall infarct	136	74
7 M	54	M	Posterior wall infarct; terminal azotemia; shock	101	...	143	...	64	35	X*
8 B	40	M	Posterior wall infarct; gastroin- testinal hemorrhage, cause unknown	...	72	103	102	115
9 C	63	M	Anterior wall infarct; broncho- genic carcinoma	195	216	200
10 E	61	F	Anterior wall infarct	78	84	93
11 H	70	F	Posterior wall infarct	148	X*
12 C	72	F	Anterior wall infarct	153	169	X*
13 G	35	M	Posterior wall infarct	105	...	104	99	70
14 B	52	M	Myocardial infarct	112	X*
15 Z	53	M	Anterior wall infarct	100	118	X*
16 G	60	M	Lateral wall infarct	70	X*	118	119	...	113
17 R	66	M	Anterior wall infarct	...	98	...	117
18 H	56	M	Posterior wall infarct	114	111	122	X*
19 W	63	M	Posterior wall infarct	91	...	118
20 C	60	M	Posterior wall infarct	97	...	120	108
21 K	63	M	Posterior wall infarct	155
22 S	49	M	Myocardial infarct, atypical	42	66	...	57	...	54	29	...	39
23 L	54	M	Myocardial infarct	105	91

* X = expired.

In this series one patient, who entered the hospital with acute anterior wall myocardial infarction, was of unusual interest because he had another myocardial infarction on the twelfth hospital day. This was confirmed later at autopsy. In this case

of these patients had developed a myocardial infarction. Two patients with paroxysmal tachycardia had normal serum mucoprotein values despite the findings of a rapid sedimentation rate in both. One patient with chest pain due to neuro-

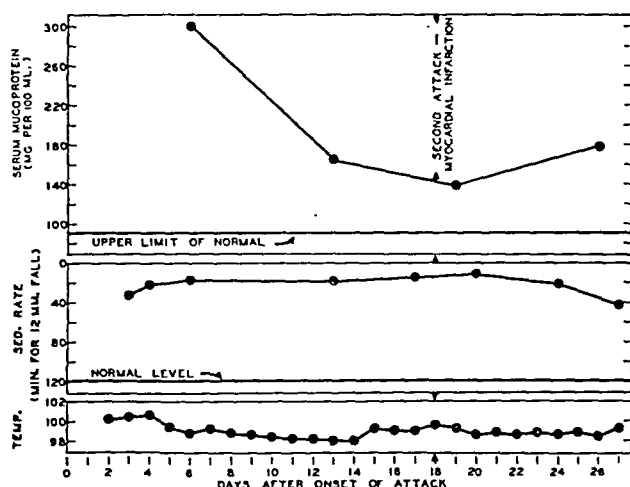


FIG. 6. Graph illustrating serum mucoprotein values following two myocardial infarctions. M. B., a fifty-nine year old white male, was admitted to the hospital with recent myocardial infarction of the anterior wall. Serum mucoprotein which was greatly elevated on admission was returning toward normal when the patient had a second attack of chest pain on the eighteenth day. Serum mucoprotein rose again and the electrocardiographic changes were indicative of a new posterior wall infarction. The patient died on the fortieth day after the initial attack. At autopsy an older anterior wall infarction and a recent posterior wall infarction were found. Again, no correlation between the serum mucoprotein and sedimentation rate (Linzenmeier) was found.

there was a marked rise in serum mucoprotein following the occurrence of each infarct. This is illustrated in Figure 6.

Serum Mucoprotein in Other Conditions Characterized by Chest Pain. Serial serum mucoprotein determinations were obtained in twelve patients who had prolonged attacks of chest pain due to causes other than myocardial infarction. Eight patients had angina pectoris or possibly myocardial ischemia without necrosis. In five of these patients serum mucoprotein determinations were performed after the occurrence of chest pain which was much more prolonged than usual. In all cases the serum mucoprotein levels were normal and did not change on subsequent determinations. Subsequent electrocardiographic and clinical findings failed to provide evidence that any

circulatory asthenia showed no elevation of serum mucoprotein as did one patient with hypertension and chest pain on the basis of fibrositis. These cases show that serum mucoprotein values are normal and remain normal in patients with chest pain due to causes other than myocardial infarction or conditions not characterized by tissue destruction.

Serum Mucoprotein Findings in Miscellaneous Conditions. In addition to serum mucoprotein determinations in a control group of normal individuals, hospitalized patients with a variety of diseases were selected at random and tested. Normal serum mucoprotein values were found in patients with such diseases as hyperthyroidism, peptic ulcer, chronic brucellosis, splenomegaly of unknown etiology, temporal arteritis, ure-

mia, cerebral thrombosis, obstructive jaundice and urinary tract infection. Elevated serum levels were found in two cases of pneumonia, in three postoperative patients and in one case of bronchogenic carcinoma. Winzler in concurrent studies³ found increased serum concentrations of mucoprotein in patients with pneumonia and with cancers. Abnormally low values for serum mucoprotein were found in a few patients with portal cirrhosis and infectious hepatitis and in one pregnant woman.

Relationship of Serum Mucoprotein to the Sedimentation Rate. In this study no constant relationship between the sedimentation rate and serum mucoprotein concentration was discernible. In patients with myocardial infarction acceleration of the sedimentation rate generally persisted longer than the elevation of serum mucoprotein. Figures 2, 4 and 5 illustrate cases of myocardial infarction in which there was absolutely no relationship between the serum mucoprotein concentration and the sedimentation rate. In a few cases of myocardial infarction there was a parallelism in the observed changes in the serum mucoprotein and the sedimentation rate. An example of this is shown in Figure 3.

In the group of twelve patients with chest pain due to causes other than myocardial infarction four patients exhibited accelerated sedimentation rates although in each of these patients the serum mucoprotein concentration was normal. Two of these patients had angina pectoris and two had paroxysmal tachycardia. Again it is apparent that no relationship exists between the sedimentation rate and serum mucoprotein level.

In Vitro Studies of Effect of Mucoprotein on Sedimentation Rate. Since it was possible that increased concentrations of serum mucoprotein could contribute to acceleration of the sedimentation rate, *in vitro* experiments were conducted to determine the effect of this mucoprotein component on the sedimentation rate. Known amounts of this mucoprotein material obtained from

pooled human plasma* were added to blood withdrawn from each of three normal individuals. Aliquots of the blood obtained from each person were prepared to contain varying concentrations of mucoprotein ranging from 50 to 850 mg. per 100 ml.

TABLE II
EFFECT OF ADDED MUCOPROTEIN ON SEDIMENTATION RATE

Subject	Serum Mucoprotein (mg. per 100 ml.)	Mg. Mucoprotein Added per 100 ml. Whole Blood					
			0	100	200	400	800
C. R. (M)	56	ESR *	20	25	24	32	42
		PCV †	48	48	48	43	41
		CSR ‡	20	26	25	26	32
H. B. (M)	47	ESR	22	20	26	29	39
		PCV	46	47	45	44	41
		CSR	21	20	23	25	32
E. F. (F)	63	ESR	18	19	23	29	43
		PCV	42	42	42	39	36
		CSR	18	19	23	24	32

* Estimated sedimentation rate.

† Packed cell volume, per cent.

‡ Corrected sedimentation rate (Wintrobe).

blood. A Wintrobe sedimentation rate determination was made with each of these blood samples. The results are shown in Table II. It was found that blood mucoprotein concentrations less than 150 mg. per 100 ml. had no effect on the sedimentation rate. In concentrations between 150 and 250 mg. per 100 ml. the mucoprotein material exerted a minimal effect upon acceleration of the sedimentation rate, and concentrations above 400 mg. per 100 ml. had a pronounced accelerating effect on the sedimentation rate. These findings were valid for both the uncorrected and corrected sedimentation rates.

These results show that the sedimentation rate is not affected to any appreciable extent by the increased concentrations of mucoprotein usually found in the serum following myocardial infarction. The acceleration of the sedimentation rate often noted in this

* A sample of lyophilized mucoprotein obtained from pooled human plasma was provided through the kindness of Dr. Richard Winzler.

condition is undoubtedly caused by chemical changes in the blood other than that reported here.

COMMENTS

The nature of the metabolic changes occurring in patients with myocardial infarction has received little study. Recently Altschule et al.⁶ reported several observations on metabolic changes in patients with myocardial infarction. Their findings, in addition to our own reported in this communication, suggest the desirability of further biochemical studies in patients with myocardial infarction.

On the basis of the preliminary studies presented herein the increase in the concentration of serum mucoprotein following myocardial infarction appears to be a fairly regular phenomenon and one which at times may be useful as an aid in establishing the diagnosis of recent myocardial infarction. Moreover, this procedure has also proved helpful in ruling out the occurrence of myocardial infarction following a bout of chest pain. No increase in serum mucoprotein was observed in patients with chest pain due to angina pectoris, paroxysmal tachycardia, neurocirculatory asthenia and fibrositis. Increases were found, however, accompanying chest pain associated with bronchogenic carcinoma and pneumonia.

In the small number of cases studied thus far the serum mucoprotein findings appeared to correlate more closely with the presence or absence of myocardial infarction than the sedimentation rate. In several cases rapid sedimentation rates were obtained in patients with angina or paroxysmal tachycardia, but the serum mucoprotein concentration remained unchanged. Conversely, one patient with fresh anterior wall myocardial infarction did not exhibit a rapid sedimentation rate until the seventh day after the onset of illness although his serum mucoprotein level was elevated on the second day. Examination of some of the graphs of individual patients shows that the serum mucoprotein values and sedimentation rates were independent of

each other although in several instances they paralleled each other.

In vitro experiments on the relationship of the mucoprotein material to the sedimentation rate showed that serum mucoprotein in concentrations usually found after a myocardial infarction had little or no influence on the acceleration of the sedimentation rate. A marked accelerating effect on the sedimentation rate does not occur until concentrations are reached which are far beyond the usual elevated pathologic values. The explanation for the effect of very high concentrations of the mucoprotein component on the sedimentation rate may be that because this material is a macromolecular substance (molecular weight approximately 50,000) it, like other macromolecular substances, accelerates the sedimentation rate.^{7,8}

Since this mucoprotein component has little or no influence on the sedimentation rate, an investigation of the changes in the protein components of the serum following myocardial infarction would be of great interest. In this connection Shedlovsky and Scudder⁹ have reported the electrophoretic findings in two cases of myocardial infarction at one week and at six weeks after the onset of infarction. They found increases in the alpha globulin fraction.

When this study was begun, it was hoped that a substance specific for the breakdown of infarcted heart muscle could be found in the blood or urine. Serum mucoprotein is *not* a specific product of the death of cardiac muscle alone. Increases in the serum mucoprotein have been found in other conditions. For example, in this laboratory elevated serum mucoprotein levels were also obtained in postoperative patients and in patients with cancer and pneumonia. Earlier workers¹⁰ have reported unusually high polypeptide* concentrations in the

* The chemical methods employed by previous workers to measure serum polypeptide or proteose concentrations are similar in principle to the method employed in this study; hence, it is possible that the determinations of serum polypeptide, proteose and mucoprotein by the various authors are all determinations of essentially the same serum protein constituent.

blood as a result of acute hepatic insufficiency, burns, trauma and cancer. Excretion of proteoses in the urine has been described in various allergic states.^{11,12} Winzler and Burk confirmed and extended the observations of earlier workers who found elevated serum protease* levels in patients and animals with cancer. In studies on the rat they also found increased serum protease levels in acute and chronic infections such as pneumonia, chronic cecitis, in advanced pregnancy and as a consequence of severe tissue injury or shock. Selye¹³ mentions the increase in blood polypeptides as one of the changes found in the "alarm reaction." All of these observations certainly point to the fact that the elevation of serum mucoprotein is a non-specific phenomenon which is the result of a variety of causes. However, there appears to be one common denominator present in every condition characterized by an increase in serum mucoprotein: a breakdown of tissue proteins. Selye emphasizes this viewpoint when he states that "the extensive protein breakdown characteristic of the shock phase of the alarm reaction is probably the cause of the increase in polypeptides."

Although this study was undertaken with the view that serum mucoprotein was derived from the breakdown of tissue proteins, there is no direct proof as yet that this is true and there are other theories¹⁴⁻¹⁶ concerning the origin of this material: (1) failure of the liver to metabolize the normal amounts of mucoprotein formed, (2) failure of the kidney to excrete them normally and (3) degradation of plasma proteins. It is unlikely that a failure in liver function can account for the elevation in serum mucoprotein found in these and other studies because we have found very low serum mucoprotein values in patients with acute infectious hepatitis or with advanced Laennec's cirrhosis. It is believed that renal insufficiency is not a factor in the elevation of serum mucoprotein inasmuch as we have obtained normal values in two patients in the terminal phase of uremia. At present

studies to determine the origin of serum mucoprotein are being conducted by Winzler.²

Further studies on the detection of other breakdown products of infarcted heart muscle which may be more specific are contemplated in this laboratory. At the present time this appears to be a fruitful field of endeavor.

SUMMARY AND CONCLUSIONS

1. In twenty-three patients with recent myocardial infarction, serum mucoprotein values were consistently found to exceed the normal range of 40 to 90 mg. per 100 ml. The actual rise above each patient's presumed normal value varied from 22 to 160 mg. per 100 ml.

2. A characteristic rise and fall of serum mucoprotein followed the clinical onset of symptoms. Serum mucoprotein was definitely elevated by the third day after clinical indications of coronary occlusion with myocardial infarction were evident. The peak of the rise occurred on the sixth day and this elevation was usually maintained for another week after which the serum mucoprotein gradually declined and approached normal values at the end of a month.

3. Serum mucoprotein values in patients with chest pain due to causes other than myocardial infarction were within the normal range in cases including angina pectoris, paroxysmal tachycardia, neuro-circulatory asthenia, hypertension and fibrositis. No increase was found by single or serial determinations.

4. In the present study no consistent relation was found between the sedimentation rate and serum mucoprotein. In general, accelerated sedimentation rates persisted longer than elevated serum mucoprotein following myocardial infarction. In several patients with angina pectoris and paroxysmal tachycardia the sedimentation rate was increased whereas the serum mucoprotein was normal.

5. *In vitro* studies on the effect of added mucoprotein upon the sedimentation rate

* See footnote on page 742.

of normal blood showed no marked acceleration until a concentration of proteose exceeding 400 mg. per 100 ml. was obtained, concentrations beyond the usual values in myocardial infarction. It is obvious then that other factors are responsible for development of the rapid sedimentation rate observed in myocardial infarction and that serum mucoprotein is not another measure of the sedimentation rate.

6. In the cases reported in this study the increase in serum mucoprotein appeared to reflect more accurately than the sedimentation rate or leukocyte count the presence or absence of myocardial necrosis.

7. Although serum mucoprotein changes following myocardial infarction are not specific for this condition alone, determination of serum mucoprotein may be useful as a diagnostic aid in evaluation of clinical syndromes caused by coronary artery disease.

Acknowledgment. We are indebted to Dr. Richard Winzler for his valuable advice and cooperation in the performance of this study.

REFERENCES

1. WINZLER, R. J. and BURK, D. Blood proteose and cancer. *J. Nat. Cancer Inst.*, 4: 417, 1944.
2. WINZLER, R. J. Personal communication.
3. WINZLER, R. J., SILBER, J. R. and SMYTHE, I. M. To be published.

4. WINTROBE, M. M. and LANDSBERG, J. W. A standardized technique for the blood sedimentation test. *Am. J. M. Sc.*, 189: 102, 1935.
5. LINZENMEIER, G. Eine neue Schwangerschaftreaktion und ihre theoretische Erklärung. *Zentralbl. f. Gynäk.*, 44: 816, 1920.
6. ALTSCHULE, M. D. and ROSENFELD, F. M. Increased catabolism following acute myocardial infarction. *Arch. Int. Med.*, 80: 74, 1947.
7. HUEPER, W. C. Macromolecular substances as pathogenic agents. *Arch. Path.*, 33: 267, 1942.
8. LEVINE, M. G. and HOYT, R. E. The use of pectin and gelatin in the processing of plasma in the blood bank. *Am. J. Clin. Path.*, 16: 40, 1946.
9. SHEDLOVSKY, T. and SCUDDER, J. A comparison of erythrocyte sedimentation rates and electrophoretic patterns of normal and pathological human blood. *J. Exper. Med.*, 75: 119, 1942.
10. LIEGEOIS, F. and TERACHE, P. Polypeptidémie normale et pathologique. Syndrome polypeptidotoxique. *Ann. de méd. vet.*, 82: 193, 1937.
11. ORIEL, G. H. and BARBER, H. W. A proteose in the urine excreted in anaphylactic and allergic conditions. *Lancet*, 2: 231, 1930.
12. ORIEL, G. H. Further observations on the biochemistry of asthmatic conditions with special reference to the urinary "proteose." *Lancet*, 2: 406, 1933.
13. SELYE, H. The general adaptation syndrome and the diseases of adaptation. *J. Clin. Endocrinol.*, 6: 117, 1946.
14. FIESSINGER, N. L'intoxication par les polypeptides. *Presse méd.*, 42: 1787, 1934.
15. CRISTOL, P. A propos d'articles récents sur l'intoxication par les polypeptides. *Presse méd.*, 43: 1107, 1935.
16. BRDICKA, R., NOVAK, F. V. and KLUMPAR, J. Critical examination of the polarographic test for cancer in deproteinized sera. *Acta radiol.*, 2: 27, 1939.

Clinical Value of Serum Polysaccharide Determinations by the Tryptophane-Perchloric Acid Reaction*

HAROLD L. ISRAEL, M.D., MARIE B. WEBSTER, M.D.† and IRENE E. MAHER, M.D.
Philadelphia, Pennsylvania

ALTHOUGH normal human serum is known to have a polysaccharide content equal to or greater than its glucose content, the polysaccharides, which are measured with difficulty, have not been completely identified. The polysaccharide concentrations in pathologic sera have been studied in a few instances in the past and elevated values were reported in patients with carcinoma,¹ pneumonia² and other infections.³

Renewed interest in this subject has recently been stimulated by investigations in diverse fields. Seibert's electrophoretic studies⁴ in tuberculosis, Winzler's polarographic studies⁵ in carcinoma and Meyer's studies⁶ of hyaluronic acid have led these investigators to the study of glycoproteins and their carbohydrate components.

The total polysaccharide of normal human serum has been found by Shetlar, Foster and Everett⁷ and by Seibert⁸ to range from 80 to 130 mg. per cent. Seibert⁹ has reported elevated polysaccharide levels in the sera of patients with advanced active tuberculosis and with carcinoma. Winzler,¹⁰ studying mucoprotein concentrations, reported increased serum levels in patients with carcinoma and pneumonia while Prinzmetal et al.¹¹ found the concentration of proteoses (containing 25 per cent carbohydrate) increased in patients with acute myocardial infarction.

In an attempt to distinguish the polysaccharides derived from a breakdown of

nucleoproteins, which might more specifically reflect tissue destruction, Seibert¹² adapted for use on serum the tryptophane-perchloric acid reaction which Cohen¹³ had developed for detection of the carbohydrate of desoxyribonucleic acid. This test, which is simple enough for routine use in clinical laboratories, gave both in experimental rabbit tuberculosis¹⁴ and in patients with tuberculosis, results which showed a highly significant correlation with extent and activity of the disease. Although the identity of the polysaccharides measured by the tryptophane-perchloric acid reaction remains uncertain, Seibert's observations on the clinical value of application of this test in tuberculosis led to the present attempt to determine its value on a general hospital service. A survey of representative patients has been made and the results of tryptophane-perchloric acid tests have been correlated with clinical, pathologic and other laboratory findings, with special interest in ascertaining whether serum polysaccharide determinations provided information of clinical value greater than that obtainable with the sedimentation rate and with routine serum protein studies.

MATERIAL AND METHODS

Determinations were made on 102 specimens from ninety patients and six healthy controls. Patients were selected from the wards of the Woman's Medical College Hospital, the Philadelphia General Hos-

* From the Department of Medicine, The Woman's Medical College of Pennsylvania and the Philadelphia General Hospital, Philadelphia, Pa.

† Now at The University Hospital, Madison, Wisconsin.

pital and the Philadelphia Hospital for Contagious Diseases in an attempt to encompass a variety of disorders. Samples of blood (6 to 8 cc.) were obtained, not under fasting conditions, centrifuged and the serum obtained and placed in a deep freeze unit. Ten sera, each in triplicate, were

units with a mean of 60 ± 12.9 units. Combining these control groups gives a mean of 58 ± 12.4 Klett units. Values within two standard deviations of this mean, that is values less than 83 units, have been considered in this study to fall within the normal range.

TABLE I
SERUM POLYSACCHARIDES, SEDIMENTATION RATES AND SERUM PROTEINS

Diagnosis	No. of Patients	Serum Polysaccharides (Klett units) (mean)	Sedimentation Rate (mean)	Serum Albumin (mean)	Serum Globulin (mean)
Neoplasms.....	10	103.5 ± 32.3	51.0 ± 5.5	3.6 ± 1.4	3.1 ± 1.1
Chronic infections.....	14	103.5 ± 26.8	33.6 ± 23.7	4.1 ± 1.8	2.3 ± 0.7
Hyperthyroidism.....	4	97.2 ± 15.8	45.0 ± 14.8	4.3 ± 2.2	2.2 ± 0.4
Cardiovascular disease.....	14	92.2 ± 23.2	35.7 ± 18.5	3.8 ± 1.6	2.6 ± 0.7
Rheumatic fever.....	5	80.0 ± 18.2	31.0 ± 26.8	4.9 ± 2.1	2.7 ± 0.5
Hepatic disease.....	7	79.6 ± 26.6	44.7 ± 9.5	3.3 ± 1.2	3.2 ± 0.3
Acute infections.....	15	79.0 ± 22.7	39.4 ± 18.7	4.0 ± 1.5	2.5 ± 0.4
Miscellaneous disorders.....	14	77.0 ± 16.2	35.0 ± 17.4	3.9 ± 1.9	2.2 ± 0.3
Pregnancy.....	7	64.6 ± 10.6	49.0 ± 5.0		
Normal subjects.....	6	47.3 ± 6.2	13.1 ± 5.6		

run at one time according to Seibert's modification¹² of Cohen's method. The mean of the three values was recorded as the final result. Because of doubt as to the nature of the polysaccharides measured, conversion to more specific terms has not been attempted and results are expressed in Klett units, as suggested by Seibert.

Simultaneous oxalated specimens of blood were obtained for sedimentation rate determinations by the Wintrobe method, which were performed within three hours of collection. Correction for anemia was not made. Serum albumin and globulin determinations were performed by the clinical laboratories of the hospitals, employing the method of Kingsley.¹⁵

RESULTS

A group of six healthy controls gave polysaccharide levels by the tryptophane-perchloric acid reaction ranging from 41 to 57 Klett units with a mean of 47.3 ± 6.2 units. (Table I.) Seibert¹² found among thirty normal persons a range from 32 to 79

In a group of seven obstetric patients, three antepartum and four immediately postpartum, six had values ranging from 55 to 70; the seventh had a level of 87 Klett units. In all of the obstetric patients the sedimentation rate was extremely rapid. Among the eighty-three patients with a variety of diseases of varying severity fifty-one had levels of 83 Klett units or more and thirty-three had levels below this value. High values were obtained (Table I) in patients with chronic infections, neoplasms, hyperthyroidism and cardiovascular disease. Less marked elevation was noted in patients with rheumatic fever, hepatic disease, acute infections and in a miscellaneous group including patients with gastrointestinal, hematologic, genito-urinary and dermatologic disorders.

Figure 1 indicates the lack of significant correlation between the serum polysaccharide levels and the sedimentation rate determinations. Similar analyses show absence of correlation between the polysaccharide levels and serum albumin, serum

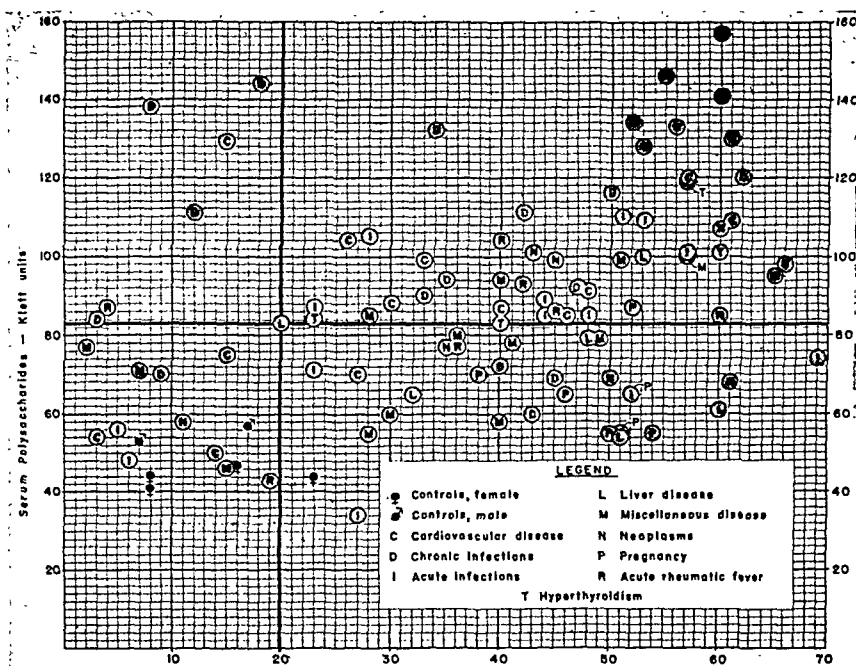


FIG. 1. Serum polysaccharides and the sedimentation rate (Wintrobe), mm. per hour uncorrected.

globulin and hemoglobin concentrations and leukocyte counts.

Neoplasms. Ten patients with histologic diagnoses of neoplasm were studied, three patients with carcinoma of the gastrointestinal tract, one of the bladder, one of the cervix and one of the larynx, as well as three patients with lymphoblastoma and one with neurofibroblastoma. Seven showed elevated polysaccharide values with the highest values, 141, 146 and 157, in the patients with gastrointestinal carcinoma. Three patients, two with carcinoma and one with lymphoblastoma, had values below 70. Sedimentation rates were rapid in all instances except in the patient with lymphoblastoma and with normal polysaccharide level. Serum protein studies revealed in most patients of this group depressed albumin levels and increased globulin levels. No correlation between these changes and those in polysaccharide content was noted.

Chronic Infections. Abnormal Klett values ranging from 84 to 144 were observed in ten of fourteen patients with chronic infections. Patients with amebic hepatic abscess, chronic pulmonary abscess and meningovascular syphilis, respectively, had elevated polysaccharide levels with normal sedi-

mentation rate. Patients with active minimal tuberculosis and rheumatoid arthritis had normal polysaccharide levels and an abnormal sedimentation rate. Patients with rheumatoid arthritis, pyelonephritis, bronchiectasis, lung abscess, meningovascular syphilis and ulcerative colitis had increased polysaccharides and abnormal sedimentation rates.

Hyperthyroidism. Three patients with diffuse hyperthyroidism and one with a toxic adenoma of the thyroid were studied. All had elevated polysaccharide levels, ranging from 83 to 121 Klett units, and in all instances the sedimentation rate was abnormally rapid and the serum protein fractions normal.

Cardiovascular Disease. Of fourteen patients with cardiovascular disease ten had elevated polysaccharide levels. The four patients with malignant hypertension and the three with acute myocardial infarctions showed elevated polysaccharide levels, as did patients with decompensated rheumatic heart disease and two patients with pulmonary infarction. Normal values were observed in patients with hypertensive heart disease, benign hypertension, inactive rheumatic heart disease and syphilitic

heart disease with congestive failure. In this group sedimentation rate findings tended to parallel those of the polysaccharides.

Rheumatic Fever. Five patients with clinically active rheumatic fever were studied. Moderate elevation of the polysaccharide level was noted in four of the five patients in this group.

Hepatic Disease. Two patients with cirrhosis and one with infectious hepatitis had polysaccharide levels ranging from 83 to 130 Klett units and three patients with cirrhosis and one with homologous serum hepatitis had normal levels. In this group there was a notable lack of correlation between sedimentation rate and polysaccharide findings: the three patients with low polysaccharide levels had rapid sedimentation rates. Four of the five patients with cirrhosis had a characteristic increase in globulin and decrease in albumin concentration.

Acute Infections. Elevated polysaccharide levels were found in only eight of fifteen patients with acute infections. Patients with meningococcic meningitis. Streptococcus viridans endocarditis under treatment, hemolytic influenzae pneumonia, mumps and rubeola showed normal levels ranging from 48 to 74, while patients with pneumococcal pneumonia and meningitis, scarlet fever, rubeola, Friedländer's pneumonia and typhoid fever showed values ranging from 89 to 115. In this group the sedimentation rate was usually increased out of proportion to the polysaccharide elevation; in no instance in this group of patients was the sedimentation rate normal in the presence of abnormal polysaccharide levels.

Miscellaneous Diseases. In this group, which includes patients with hematologic, gastrointestinal, genito-urinary and dermatologic disorders as well as several instances of minor illnesses in which a definite diagnosis was not established, elevation of the polysaccharides was infrequent: only five of fourteen patients had abnormal values. Six of the nine patients with low polysaccharide levels had elevated sedimentation rates.

COMMENTS

Although the tryptophane-perchloric acid reaction was employed by Seibert originally to detect desoxyribonucleic acid, subsequent investigation revealed that the carbohydrate measured by this test in normal and pathologic sera was not a single substance. Detailed analysis¹² suggested that the polysaccharide measured might be a mixture of desoxyribonucleic and ribonucleic acids and their derivatives, a fructose complex, or even a carbohydrate-protein complex similar to the mucoprotein under investigation by Winzler. An important advantage of this test over those used for determination of total serum polysaccharide content is its ease of performance which permits its use as a routine procedure in general hospital laboratories. Seibert^{1,12} found elevated polysaccharide concentrations to be correlated with increases of alpha-2 globulin in the sera of patients with tuberculosis and carcinoma. Whether the increased polysaccharides observed in the sera of patients in this study with neoplasms, chronic infections, hyperthyroidism and cardiovascular disease are related to increases in alpha-2 globulin is not known, since electrophoretic analyses were not available. No correlation was observed between the polysaccharide content of sera and the albumin and globulin concentrations as measured by ordinary clinical laboratory methods.

Special interest exists in comparison of the tryptophane-perchloric acid reaction with the sedimentation rate, which has found a wide field of usefulness because of its simplicity. The sedimentation rate has become firmly established as a valuable aid in the study of arthritis, tuberculosis and in general medicine, even though the mechanism underlying acceleration of erythrocyte sedimentation is not definitely known. Gutman¹⁶ has recently reviewed the conflicting evidence concerning the relation of sedimentation and serum protein alterations and has concluded that an increase in fibrinogen content of serum plays a major role and increases in alpha,

beta and gamma globulins play a lesser role in accelerating sedimentation of erythrocytes; a decrease in serum albumin enhances the rate of sedimentation. Meyer¹⁷ has suggested that accelerated sedimentation may be due to increased amounts of glycoproteins in the serum and has demonstrated that the addition to serum of hyaluronic acid, a mucopolysaccharide, markedly increases the rate of sedimentation. In the clinical material studied in the present investigation, however, sera with high polysaccharide content as shown by the tryptophane-perchloric acid reaction often did not exhibit rapid sedimentation rates. Conversely, patients with extremely rapid sedimentation rates, e.g., in pregnancy, frequently showed low polysaccharide levels. Gutman¹⁶ has pointed out that different protein changes may be responsible for the rapid sedimentation rates of acute infections and those of chronic infections. The observations in the present report indicate that serum polysaccharide determinations may have clinical value in the differentiation of acute and chronic infections.

The sedimentation rate is of limited value in obstetric practice because rapid sedimentation is almost invariably present during pregnancy and the postpartum period; the serum polysaccharides are apparently rarely elevated in uncomplicated pregnancy and their determination may prove useful in the detection of intercurrent diseases.

The sedimentation rate is used frequently as a means of excluding serious disease. For this purpose the tryptophane-perchloric acid reaction appears to be a valuable corroborative test. Patients in the present study with normal sedimentation rates and normal serum polysaccharide levels rarely proved to have a serious disease.

SUMMARY

1. Seibert's modification of the tryptophane-perchloric acid reaction has been employed to determine serum polysac-

charide levels in a survey of general hospital patients.

2. Elevation of the serum polysaccharides was most marked and frequent in patients with neoplasms, chronic infections, hyperthyroidism and cardiovascular diseases. Abnormal values were less often observed in patients with acute infections, hepatic disease, rheumatic fever and miscellaneous disorders. Normal values were the rule in pregnancy.

3. Serum polysaccharide elevation appears to reflect biochemical changes different from those measured by sedimentation rate and other routine laboratory studies.

Acknowledgments: The assistance of Florence B. Seibert, Ph. D., Associate Professor of Chemistry, Henry Phipps Institute of the University of Pennsylvania and her staff and that of Phyllis Bott, Ph. D., Professor of Physiological Chemistry, the Woman's Medical College, and her staff are gratefully acknowledged.

Financial aid from the Anonymous Fund of the Woman's Medical College is also gratefully acknowledged.

In addition thanks are due to the Research Committee of the Philadelphia Hospital for Contagious Diseases for permission to study patients with acute contagious diseases.

REFERENCES

1. LUSTIG, B. and LANGER, A. Über die Bestimmung und den Gehalt an freiem Eiweiss- und gebundenem Nicht-eiweisszucker im normalen und pathologischen Serum, Liquor und Harn. *Biochem. Ztschr.*, 242: 320, 1931.
2. NILSSON, I. Über den Glucosamingehalt des Blutserums bei Gesunden und Pneumoniekranken. *Biochem. Ztschr.*, 291: 254, 1937.
3. WEST, R. and CLARKE, D. H. The concentration of glucosamine in normal and pathological sera. *J. Clin. Investigation*, 17: 173, 1938.
4. SEIBERT, F. B., NELSON, J. W. and SEIBERT, M. V. Correlation of extent of tuberculosis with amount of polysaccharide in the serum. *Proc. Soc. Exper. Biol. & Med.*, 52: 219, 1943.
5. WINZLER, R. J., DEVOR, A. W., MEHL, J. W. and SMYTH, I. R. Studies on the mucoproteins of human plasma. 1. Determination and isolation. *J. Clin. Investigation*, 27: 609, 1948.
6. MEYER, K. Mucoids and glycoproteins. *Adv. Protein Chem.*, 2: 249, 1945.
7. SHETLAR, M. R., FOSTER, J. V. and EVERETT, M. R. Determination of serum polysaccharides by the

- tryptophane reaction. *Proc. Soc. Exper. Biol. & Med.*, 67: 125, 1948.
8. SEIBERT, F. B. and ATNO, J. Determination of polysaccharide in serum. *J. Biol. Chem.*, 163: 511, 1946.
 9. SEIBERT, F. B., SEIBERT, M. V., ATNO, J. and CAMPBELL, H. W. Variation in protein and polysaccharide content of sera in the chronic diseases, tuberculosis, sarcoidosis, and carcinoma. *J. Clin. Investigation*, 26: 90, 1947.
 10. WINZLER, R. J. and SMYTH, I. M. Studies on the mucoproteins of human plasma. II. Plasma mucoprotein levels in cancer patients. *J. Clin. Investigation*, 27: 617, 1948.
 11. SIMKIN, B., BERGMAN, H. C. and PRINZMETAL, M. Studies on coronary circulation. v. Quantitative changes in a serum mucoprotein following the occurrence of myocardial infraction. *Am. J. Med.* 6: 734, 1949.
 12. SEIBERT, F. B., PFAFF, M. L. and SEIBERT, M. V. A serum polysaccharide in tuberculosis and carcinoma. *Arch. Biochem.*, 18: 279, 1948.
 13. COHEN, S. S. Observations on the estimation of desoxyribose nucleic acid. *J. Biol. Chem.*, 156: 691, 1944.
 14. SEIBERT, F. B. Personal communication.
 15. KINGSLEY, G. R. The direct biuret method for the determination of serum proteins as applied to photoelectric and visual colorimetry. *J. Lab. & Clin. Med.*, 27: 840, 1942.
 16. GUTMAN, A. B. The plasma proteins in disease. *Adv. Protein Chem.*, 4: 156, 1948.
 17. MEYER, K., HAHNEL, E. and FEINER, R. R. Experiments on erythrocyte sedimentation rate. *Proc. Soc. Exper. Biol. & Med.*, 58: 36, 1945.

What Can We Learn from a Medical History?*

CARL BINGER, M.D.†

New York, New York

EXPERIENCE teaches most of us that time spent in obtaining a careful medical history is time well spent and will save wasted motions later. What we actually can learn will depend, of course, on our skill and on the patient's willingness and capacity to cooperate with us. Although I shall discuss both of these topics later, it will be more appropriate to consider first what we should aim at when taking a medical history.

Naturally this will depend on our purpose. As I understand it the purpose of taking a medical history is to record a series of events that have culminated in the illness or disorder for which the patient has consulted us. It is assumed that from such a record we shall get some understanding of the sick person and of his ailment and, furthermore, that others trained in medicine will derive a similar understanding from reading the history that we have written down.

No medical history, however, can reproduce accurately what occurs in nature. It is at best a kind of stylized symbolic representation of certain human experiences in much the same way that a map is a stylized symbolic representation of a landscape. The value of a good map will depend upon the accuracy of its scale and upon the picturing of the relationship of certain important land masses, contours, bodies of water, as well as certain man-made structures such as railroads and large settlements. With the aid of such a map, we can find our way around in strange country. But if the map depicts every culvert, duck pond and hot dog stand and leaves out

mountain ranges and navigable rivers, we will soon go astray if we rely upon it. Just so a good medical history will portray in the dimension of time, rather than space, the influences, past and present, that are important in the development of the patient and his disorder. You may justifiably catch me up on the word *important*. There is no question about the importance of a mountain range or a navigable river but who is to say what is important in the record of a patient's life. If we depend wholly on his judgment, then of what use is our medical knowledge; and if we depend wholly on our own preconceived notions, then we will arrive at a kind of standardized history which includes everything and tells us nothing.

When I was an intern, we were taught to take just such histories. We would approach a patient and after recording his complaint (this we were taught to put down strictly in the patient's own words, an excellent habit to which I have always clung) we would write the letters, F. H., for family history. That was quickly disposed of with: The patient's F. was I. and w. but his M. had unfortunately d. of typhoid fever. A number of S's and B's were usually I. and w. or a couple might have d'd in infancy. And then the ritual was to say that the F. H. was otherwise "non-contributory" (a truly fabulous misconception!) and that there was no tuberculosis (later we added "or known exposure") or malignant disease in the family. We would then go on to the P. H. No illness or accident would escape us. We were as persistent as a cigar-smoking detective in a movie melo-

* Presented as an informal talk before the teaching and resident staffs of the Payne Whitney Clinic (New York Hospital), N. Y.

† Associate Professor of Clinical Psychiatry, Cornell University Medical College, N. Y.

drama and about as subtle. I recall asking a young woman about her weight. What was her present weight, her weight last year and her heaviest weight? When I asked her what her lightest weight was and she said "5½ pounds"! I began to get the notion that perhaps I was boring her by the third degree method.

I recall the chief attending physician, a sober and pedestrian man, asking a little boy of eight whether the pain in his groin radiated to his penis and testicles. The child looked up bewildered and said: "What's them"?

Then with a rumble of drums came the last and final act of the circus, the P. I. This was a new event, a thing in itself, a calamity, a misfortune, an act of God like a hurricane or an earthquake. It had little to do with past events and less with what today we call the personality. Our histories were nothing if not complete. They covered pages of carefully written foolscap. The greatest sin was the sin of omission. And they bore about as much resemblance to the true story of the patient's life as a Mercator projection does to the contours of the earth's surface.

During World War I I was for a time put in charge of a large medical ward in a Base Hospital in France. Although I was only a First Lieutenant, casual officers outranking me by several grades were assigned to this ward for instruction in physical diagnosis. One of them had the habit of turning in long and rambling medical histories that stretched out interminably and arrived nowhere. I urged this officer as tactfully as I could to stick to the essentials. The next history that he wrote up was a short one. It said:

Complaint: Abdominal pain

Past history: Kicked by a steer

Diagnosis: Tonsillitis.

This has always seemed to me a paradigm of the nonsequitur and an excellent caricature of many medical histories today. For the method I have just been describing is by no means as quaint and antiquated as I have made it sound. It is the current method in

most general hospitals and in many private offices although in some, history taking is but a scanty business or is turned over to an office nurse who at the same time sizes up the patient's probable income.

Perhaps in only a few places has psychiatry made its inroads on the medical curriculum and modified this traditional way of taking histories. This is psychiatry's greatest contribution to clinical medicine, the introduction of what I have called elsewhere, scientific biography.

There is no doubt that a new type of medical history is being developed although as yet it has not been formulated and in only a few medical schools, to my knowledge, is it being deliberately taught. If such a change is occurring, it is, as I have said, largely due to the influence of modern dynamic psychiatry. But there are other reasons as well that have contributed to it.

The establishment of the germ theory of disease in the latter part of the last century set the pattern for much of the investigative work of the following half century. Koch's laws became the Magna Charta of medical research. To isolate a germ and to prove its specific pathogenicity, this was the greatest scientific achievement. And why not? When one considers the triumphs and blessings that have resulted from such studies, it was natural that this type of thinking should have dominated clinical medicine and that in large measure it still does. The successes that were achieved have, as is well known, reduced the incidence of infectious diseases and brought into relative prominence the degenerative diseases and stress reactions. To these conditions such simple unitary etiologic thinking, as exemplified by Koch's laws, seems far less applicable. We are no longer dealing with such invariable relationships as might be expressed in the statement: A acting on B produces C. Illness is not always the immutable effect of some one cause but rather the outcome of a process of development in which innumerable factors play a role. We have had to develop new theories and concepts of disease and also new methods of study.

Our aim in taking a medical history is no longer simply to find an etiologic agent and then to devise means of exorcising it. It is rather to discover what kind of individual we are dealing with, what are his strengths and weaknesses, his assets and liabilities, what his patterned reactions are under stress and in what respects do the bodily defenses, which he mobilizes, themselves turn into malign and damaging forces?

Harold Wolff¹ has put this well when he says that although man's protective activities may be life-saving if they are used in emergencies to destroy the forces that threaten him, the same protective activities when used as life-long patterns may damage the very structures they were devised to protect.

Perhaps Shakespeare had a similar principle in mind when he had Hamlet say: "Find out the cause of this effect,

Or rather say, the cause of this defect,

For this effect defective comes by cause."

Since in the modern world we are constantly being confronted by new and changing environmental situations and since the human organism has only a limited number of ways in which it can respond to these changes, it is clear that much of clinical medicine will be concerned with the problem of homeostasis. How does the organism strive to maintain a steady state, both psychologically and physiologically? Are its efforts effective and efficient? This is the general line of inquiry that a modern medical history must pursue. To do so the form of the history has to be greatly revised. We pretty much have had to give up the question and answer game which some years ago led us so securely, at least so we thought, to our goal.

A wise physician today will recognize that in a great many instances he cannot possibly know just what questions to ask and, furthermore, even if he did, the patient could not answer them. Obtaining a medical history has become primarily a personal voyage of discovery into unknown territory. Physician and patient are joined

in a common enterprise to uncover certain facts. Often the patient is a laggard and will resist progress and as often the physician, because of his own emotional blindness, will not be able to see or understand what is before him.

This is true of a medical history as well as of a psychiatric one. In my opinion there is not much difference between them except that imposed by time and by the emphasis of the immediate complaint. Since the medical history has become, or should become, more fluid and more elastic at once, no form or syllabus will really suffice, no printed list of queries against which one places check marks. These may have their value when one is engaged in a specific research project and is trying to get answers to certain set questions. Or again, printed forms may have their uses in dealing with large numbers of patients when saving of time and medical personnel is of moment. But, important as they may be, I am not concerned with them now but rather with how this new method of history taking can be described, formulated and taught.

Let us begin at the beginning. In spite of all our protestations about "the patient as a person" the young medical student still looks upon him as a case of this or that. If he does, it is our fault because we still believe in a kind of Platonic abstraction called disease as if it existed outside the body of the sufferer. The conventional and jejune introduction to most medical histories states that: "The patient is a white male sitting comfortably in bed." The student seldom knows the patient's name and if he does the national origin of the name means little to him. Actually it makes a great deal of difference whether the patient is called Mr. Feitelbaum, Mr. Finnegan or Mr. Ford. As I look over some of my own records I find such unconventional statements as Miss Smith looks like "a languid lily," "Mr. Jones looks like a snapping turtle with a gold watch chain," or again, "Mr. T. is an artist of Finnish origin but with a Yankee accent. He looks like a pink-cheeked beer barrel." You may

protest that these are unscientific statements, that they introduce a subjective element which colors the material. But do not be deceived, it is quite impossible to keep out one's subjective judgments and opinions and it is no more scientifically accurate to describe the patient as though he were a puppet or a manikin.

It would be a great benefit to medical students if we could teach them the art of history taking in medical out-patient departments and not on the wards. A bank-teller or the corner grocer's wife cease to be themselves when we rob them of their usual plumage and put them into hospital night clothes. Furthermore, they are different people when sitting opposite us in a chair from what they are when "lying comfortably" in a hospital bed. The very fact that a hospital bed is so strangely tidy and high from the ground makes them different from what they would be in their own birds-eye maple or golden oak Grand Rapids variety.

What the student should see as clearly as he can, is the patient's *persona*, i.e., what front does he present to the world? If he knows the patient's name and calls him by name, he will naturally get a more accurate picture of him because the patient will respond in a less guarded way. The student should then shake hands with the patient. This is not only a civil thing to do but much can be learned from a handshake. Does the patient present the tips of his fingers only in an uncertain and limp way? Is he a bone crusher? Are the hands wet, cold and tremulous? Does the handgrasp cling lovingly as it does in many alcoholics? Or cannot the patient release his grasp as was true of a patient I saw who was afflicted with muscular dystrophy with pronounced weakness of the extensor muscles?

Having established this contact, the student should be taught to exhibit some interest in the patient's welfare. It does not make much sense to approach a sufferer with a gastric ulcer and ask him right off the bat whether he was a breast baby or a bottle baby even if this fact is important to

ascertain. The patient should be encouraged to talk about the here and now, about what ails him. Why has he come to the hospital or come to consult the physician? Many present day patients think that they are helping us most by giving a kind of prepared historical review of their lives, beginning with their parents unhappy marriage and how they were jealous of their younger sisters. A colored cook recently said to me: "I have a terrible pain in the back but I know it's all due to my inferiority complex."

The physician must go along with such comments but gradually lead his patient to talk about what ails him. It is far better to proceed from the present backward although in the final write-up the history may be presented in reverse order. We must pay strict attention to how the patient behaves during the interview, to the language he uses, to his attitude toward his symptoms and to the anxiety with which they are associated. We must keep our ears cocked for what has been called "body language." What is the body trying to say that the patient cannot say?

During the course of such an examination we can include, without the patient's ever knowing it, some of the usual psychologic tests for memory, symbolization, logical faculty and general intelligence. We do not need to have the patient say "methodist episcopal" in order to spot a dysarthria. We must above all get some knowledge of prevailing moods and suppressed emotions which may express themselves physiologically.

As I said at the beginning what we are aiming at in taking a history is a knowledge of the person as well as of his illness because in most instances, perhaps in all, they are inextricably related. The method of what has been called "associative anamnesis"² is a useful one. The patient is encouraged to talk freely. We interrupt him to guide him into productive channels, not by interposing new questions but by picking up one of his own statements and modifying it just enough to rephrase it into a query that will serve as a new point of departure. From

the mass of material so obtained we try to reconstruct a life history. We draw a map to help us find our way, but we must never forget that the map making is a combined enterprise of patient and physician. It is for this reason, not for sentimental ones, that the physician-patient relationship is the

basis both of history taking and of subsequent therapy.

REFERENCES

1. WOLFF, HAROLD G. Protective reaction patterns and disease. *Ann. Int. Med.*, 27: 944, 1947.
2. DEUTSCH, FELIX. Associative anamnesis. *Psychoanalyt. Quart.*, 8: 354, 1939.

Fluorocardiography (Electrokymography)*

ALDO A. LUISADA, M.D. and FELIX G. FLEISCHNER, M.D.

Boston, Massachusetts

THE clinical importance of obtaining accurate records of volume changes and motions of the cardiac chambers and the large vessels is self-evident. Many clinical problems in the field of cardiology have been successfully studied by graphic methods such as cardiography, sphygmography, phlebography and esophagocardiography. However, these methods permit but indirect conclusions as to the heart action and are limited in their scope and accuracy. Roentgenologic visualization of the cardiovascular silhouette offered a new approach to more direct records. Roentgenocinematography would be a desirable method for this purpose but is too cumbersome and expensive for general use and has been supplanted by roentgenkymography,¹⁻⁹ a method screening out one or several points of the cardiac silhouette by a slitted diaphragm and moving a film in a direction perpendicular to the slits. The tracings so obtained record the movements of these particular points of the heart silhouette.

Roentgenkymography was received with great expectations but its physiologic and technical limitations were soon recognized. The inherent physiologic limitation is due largely to the fact that the visible motion of the heart is a composite of changes in volume and changes due to motion of the heart as a whole. Attempts have been made to overcome the technical limitations of roentgenkymography which consist of limited speed and recording time, lack of detail and distortion of the recorded waves. With the advent of light-sensitive electronic tubes, these served as immobile receptors for the moving x-ray films.

* From the Departments of Radiology and Medicine, Beth Israel Hospital, Boston, Mass.

THE APPARATUS

The first apparatus of this kind for practical use was developed by Henny and Boone who called their method electrokymography (1945),²³ followed by Lian and Minot (radioelectrokymography, 1946),²⁰ Marchal (kinedensigraphy, 1946)²¹ and Luisada, Fleischner and Rappaport (fluorocardiography, 1947).³¹⁻³³ These various apparatus and technics are based on a common principle although they are different in structural details, sensitivity and accuracy.

The arrangement used by Luisada, Fleischner and Rappaport³² consists of: (1) fluoroscope; (2) pick-up device attached to a fluoroscopic screen made up of a photo-multiplier tube (RCA-931-A) provided with a slitted diaphragm and a small fluoroscopic screen (Patterson B); (3) electrical arrangement to transform the incoming commercial current into direct current of staggered voltages, and a device for rapid change of degree of amplification; (4) electric filter suppressing the flicker from the x-ray tube; (5) galvanometer transcribing the tracing to a moving film; and (6) microphone to be connected with a sound recorder (of the "stethocardiette" or a similar apparatus). (Fig. 1.)

Any upright fluoroscopic stand can be used for the seated patient; for very sick patients a horizontal fluoroscopic table is necessary. Any of the commercial tilt-tables can be used for both purposes. An x-ray machine with full-wave rectification is preferable because it is easier to suppress the 120-cycle ripple by filterage. Machines with half-wave rectification can also be used with a special filter for the 60-cycle ripple.

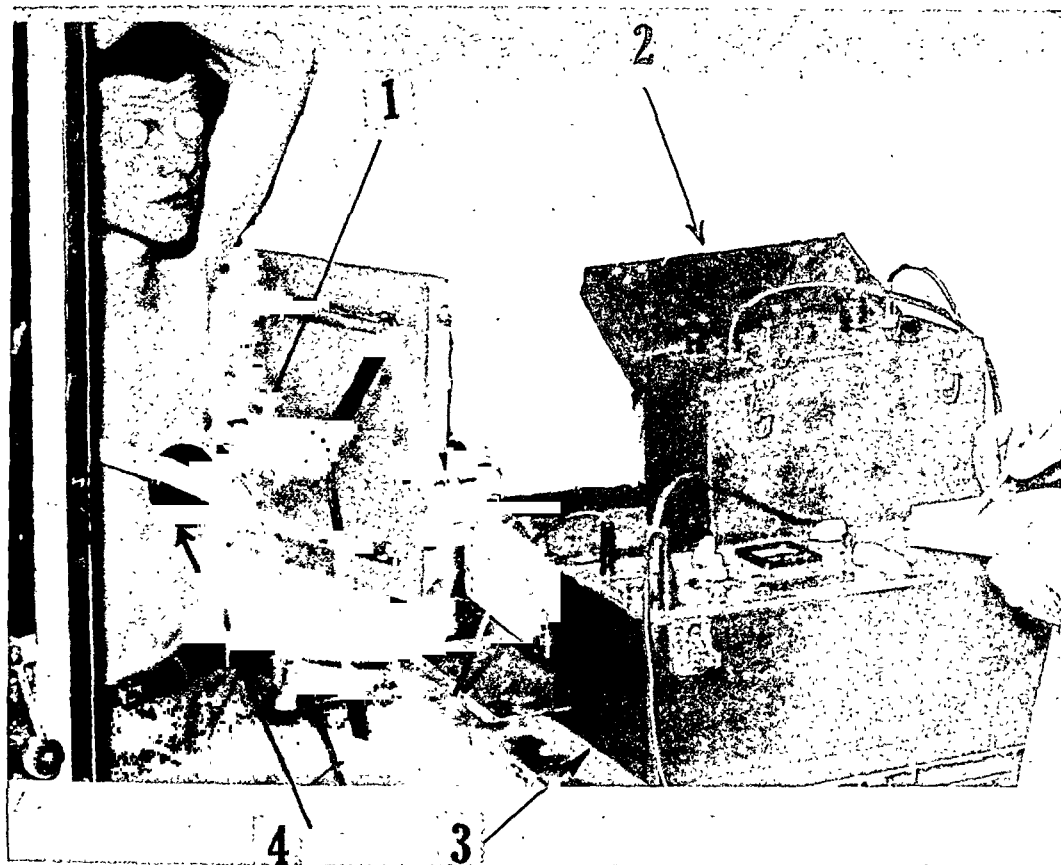


FIG. 1. Arrangement of the apparatus for fluorocardiography. (1) Pick-up unit behind the fluoroscopic screen; (2) box with regulating panel; (3) electrophonocardiograph. The patient is shown in the lateral position for recording the right ventricular tracing. (4) The microphone, placed on the precordial area, records the heart sounds.

The regulating devices described in (3) and (4) are built into a small portable box, 8 by 12 by 5½ inches. Any commercial electrocardiograph can be used. Since the authors apply the heart sounds as time reference, a "stethocardiette" (or similar apparatus) has been used as the recording machine. From the above description it is clear that most of the necessary equipment is already available in practically every hospital and in many private laboratories. The additional new equipment consists of the pick-up and regulating units, two small portable pieces of low cost.

While the classical roentgenkymograph registers the pulsating shadow directly on the film, in this new apparatus the pulsating changes of light energy, proportionate to the pulsating movements, are transformed into a pulsating electric current to be recorded by a standard electrocardiograph. This basic principle implies the possibility

of using the same device for measurements of changes of density as a densograph; when the slit is placed over the center of an opaque object, the changes of opacity of the latter will be picked up and recorded.

The polarity of the apparatus is so arranged that an increase in light causes a downward movement of the tracing. Therefore, any drop of the curve indicates either an inward motion of the cardiac border (if the slit is across the border of the cardiac silhouette) or a decrease in the thickness of the structure (if the slit is over an homogeneous area, recording a densogram), both as a result of contraction. Any wave occurring before the first large vibration of the first sound is presystolic; any wave occurring after the last vibration of the second sound in diastolic; any wave taking place between the beginning of the first sound and the end of the second is systolic.

Fluorocardiography would appear to

have the following advantages over roentgenkymography: (1) The slit can be applied perpendicularly to the section of the contour to be studied and choice of place is possible under fluoroscopic control. This is extremely important in the oblique positions and has a special value in the postero-anterior position of the patient. (2) The speed of the fluorocardiographic film is much greater and this causes an apparent spreading of the different waves. Magnification of the height of the waves can be regulated at will. These two facts permit better individualization and study of the details. Furthermore, fluorocardiographic tracings record as many cycles as desired, another fact which facilitates study. (3) The timing of the waves is obtained in a simple and accurate way by comparing the tracing with a phonocardiogram simultaneously recorded.^{32,33} (Chamberlain, Henny and Boone^{23,24} time their tracings by simultaneous records of the carotid pulse, while Lian and Minot²⁰ prefer the electrocardiogram as a time reference.) (4) Fluorocardiography permits accurate study of the auricles, ventricles and large vessels in the oblique and lateral positions. (5) Fluorocardiography, through magnification, permits accurate study of changes in opacity of various organs (densograms) thereby permitting the study of "plethysmograms" of organs like the branches of the pulmonary arteries (hilar vessels), pulmonary veins and pulmonary parenchyma which could not be studied by roentgenkymography.

The procedure is performed by a two-man team, the fluoroscopist and the electrocardiologist. The "stethocardiette," electrical unit and pick-up device being assembled and the wire connection attached, the patient is seated on a rotating stool in front of the fluoroscope. An elastic strap is slung around his chest to hold the microphone which is placed over the center of the precordium in such a way as not to overlap the cardiac borders. Transmission of the heart sounds is checked with the audiophone. The patient is then instructed how to hold his breath in a medium posi-

tion. The room is darkened as for any routine fluoroscopy, a screened pilot light illuminating the panel of the regulating unit and the electrocardiograph. With the patient in the postero-anterior position, the pick-up device is placed under fluoroscopic control in the region of the cardiac apex, the translucent slit being perpendicular to and crossing that part of the silhouette to be studied. With the slit in place and the fluoroscope in operation, the electrocardiologist regulates the amplitude of the deflections, then asks the patient to hold his breath and starts the electrocardiographic camera under constant observation and control of the light beam. After having obtained a good tracing of several heart cycles the operation is interrupted, the pick-up device moved to the next place desired and the same procedure repeated. Notes of the position of the patient, of that of the pick-up and of the degree of amplification used are made for every tracing.

A special electrical filter has been adopted for the simultaneous recording of electro- and phonocardiograms together with the fluorocardiogram in particular cases.

Several standard positions for the slit have been studied with the patient in both sitting and recumbent positions.^{33,35} (1) *Patient in postero-anterior position* (Fig. 2): Apex, mid-left ventricle and high left ventricle; pulmonary knob; aortic knob; high and low right auricle; pulmonary veins (densogram); right and left hilar shadows (densograms); high, middle and low right and left lung fields (densograms). (2) *Patient in 10 degree left oblique*: Left auricular appendage; ascending aorta. (3) *Patient in 45 to 60 degree left obliques*: Left auricle; descending aorta (densogram); high, middle and low posterior ventricular border (left ventricle). (4) *Patient in 45 degree right oblique*: Left auricle; superior vena cava; inferior vena cava (in deep inspiration); upper border of diaphragm (liver tracing); high, middle and low anterior ventricular border (left ventricle). (5) *Lateral positions* (left lateral is preferred): Anterior ventricular border (right ventricle).

In most studies the fluorocardiograms were recorded during voluntary apnea in an intermediate phase because comparative observations had shown that the pulsations of the lung (and, to a lesser extent, those of the hilar shadows and the pulmonary

coarser than any of the waves due to cardiac action. A suitable condenser introduced between the fluorocardiograph and the recording galvanometer is sufficient to modify the time constant of the apparatus. The smaller the condenser the lesser is the

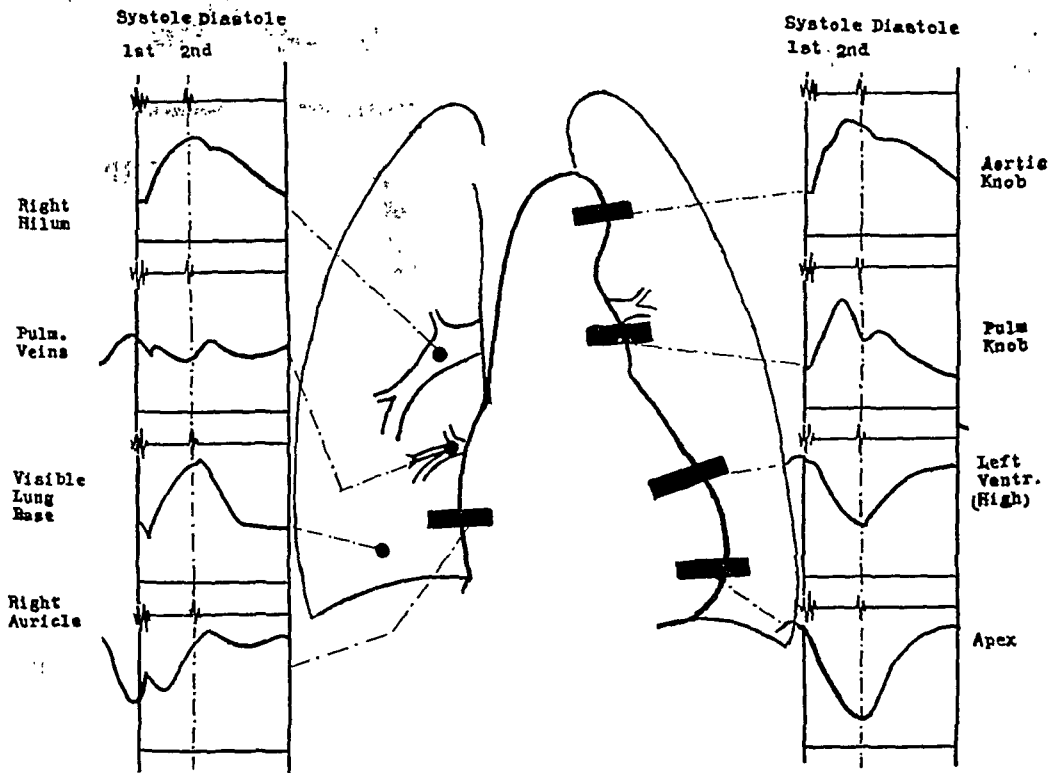


FIG. 2. Scheme of normal tracings recorded in the postero-anterior position.

artery) were greater in inspiration than in expiration. A few words of instruction usually suffice in teaching the patients to hold their breath without excessively inflating or deflating their lungs. By using this procedure, however, it was difficult to obtain reliable tracings in children and in patients with chronic diseases of the lungs, who were unable to control their respiration because of either age or dyspnea. This difficulty was overcome by the following technical means.⁴² Wandering of the base line caused by respiration may be considerably reduced by altering the electrical time constant of the apparatus. When this constant is shortened, there is a proportionally greater attenuation of the coarse waves as compared to the more rapid. Respiration is represented in the fluorocardiogram by extremely slow waves, far

electrical constant. Various size condensers, which may be selected by means of a switch, permit the operator to obtain the optimum time constant, namely, a value which produces a fluorocardiogram that does not wander off the paper.

The reduction of the electrical time constant of the apparatus does introduce a certain degree of error in the fluorocardiogram which is dependent upon the amount of reduction. The error presents itself in two forms: one is a slight error in the phase (or actual time) of registration of the component waves; the other is a slight change in the configuration. However, no elimination of the component waves which would be present under normal operating conditions was observed.

Using the above described filter comparative studies in normal subjects were

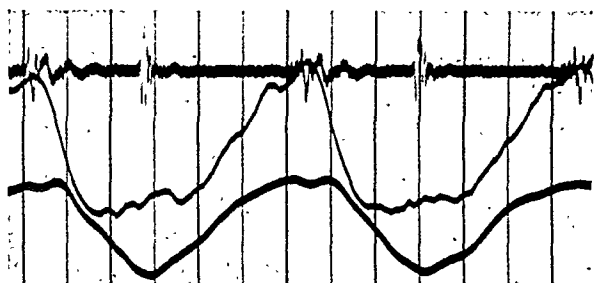


FIG. 3. Simultaneous fluorocardiograms of the apex (middle curve) and of a higher point of the left ventricular profile (lower curve). Phonocardiogram: The apical tracing initiates its drop at the beginning of the tension period while the higher ventricular tracing (lower curve) shows a notch in that phase and drops only at the beginning of the ejection period.

made.⁴² It was proven that it is possible to record the pulsations of the lungs or any other cardiovascular or pulmonary structure during normal respiration with the following precautions: (1) Whenever possible, the subject is instructed to breathe evenly and slowly, without sudden gasps. (2) The roentgenologist should observe the visible structure which is being studied and make sure that it is not moving in and out of the slit because of respiratory dynamics.

TYPICAL TRACINGS IN NORMAL SUBJECTS

The tracing of the apex³³ reveals a small positive wave due to completion of ventricular filling by the auricular contraction; a small negative wave caused by torsion of the heart during the tension period; a deep negative wave during the ejection period of systole; a rapid rise in early diastole; a slow rise during middle and late diastole. (Fig. 2.) Tracings recorded over any point outside the apex usually present somewhat smaller waves and seem to start later than the apical tracing. The last fact is due to less marked interference of motion phenomena and gives the impression that the contraction starts at the apex and spreads toward the base. (Fig. 3.) Return of the ventricular mass to its position in diastole may cause non-coincidence of the deepest point with the second sound. This phenomenon, however, is more marked at the apex and may be entirely absent. Occasionally a slow rise or a slower course, even simulating a small drop in early

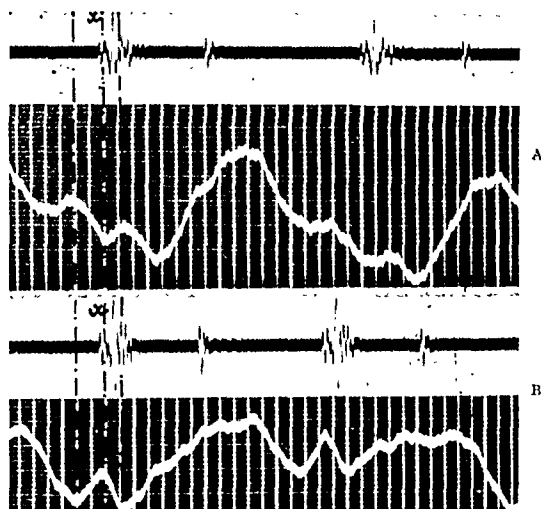


FIG. 4. A, tracing of the left auricle in the left oblique position. A negative wave is present in presystole in a normal subject because of auricular contraction. B, tracing of the pulmonary veins in the postero-anterior position in the same subject. A positive wave (*a* wave) is present during presystole. Line *x* indicates the initiation of the auricular waves (negative presystolic wave in the venous tracing).

diastole, may be seen. The latter phenomenon is probably due to positional changes. The tracings of the anterior and posterior surfaces of the left ventricle are similar to those of the lateral margin. The tracing of the right ventricle is similar to that of the left but the waves have a smaller amplitude.

Both left and right auricular tracings reveal first a deep negative wave resulting from the auricular contraction (Fig. 4A), then a second decrease of auricular volume due to ventricular traction over the A-V septum and later an early diastolic drop. If the subject is in the recumbent position, a gradual rise in the tracing of the right auricle may be seen during systole on account of the greater venous return from the inferior cava.

The tracing of the ascending aorta³⁵ reveals first a small negative wave due to traction of the left ventricle over the root of the vessel, then a rapid rise and a sustained plateau similar to a tracing of intraventricular pressure, later a high wave in diastole due to summation of the dicrotic wave with a movement of return of the vessel to its prior position. A small positive

wave may be seen occasionally in presystole due to motion of the heart at the time of auricular contraction.

The tracing of the aortic knob³³ has all the characteristics of a "central" pulse. That of the pulmonary knob presents a smaller anacrotic depression and a higher dirotic wave, often resembling the tracing of a peripheral pulse. (Fig. 5A.)

The tracing of the descending aorta³³ usually presents a rounded profile and no trace of the dirotic wave; the fact that the tracing is a densogram may explain the lack of details.

The tracing of either hilar shadows^{33,35} reveals an arterial wave which starts with a definite delay over that of the pulmonary knob; it has a rounded profile, a peak which is near the second sound and may or may not present a dirotic wave. (Figs. 2 and 5B.)

The tracing of the pulmonary parenchyma^{33,35} (Fig. 5C) is equivalent to a plethysmogram. The ascending branch of the wave is purely arterial; the rise of the wave occurs with a certain delay over that of the respective hilar vessels. On the other hand, the peak and the descending branch of the wave are deeply affected by variations in the venous filling of the lung. Actually the peak occurs soon after that vibration of the phonocardiogram which records the opening of the mitral valve. The descent of the tracing is rapid on account of the forward motion of the pulmonary venous blood toward the heart in early diastole which causes depletion of the venous network.

The pulmonary veins can be studied by applying the slit transversely over an area which is about 2 cm. outward from the convexity of the right auricle in the postero-anterior positions.³⁵ This point was indicated by Marchal²¹ as corresponding to a bundle of pulmonary veins and this was confirmed by timing the arrival of diodrast on a fluorocardiogram. A thick vascular shadow is visible at times in that area.

The arrangement of the larger vessels of the hilar region is different for the arteries and the veins. It has been known that

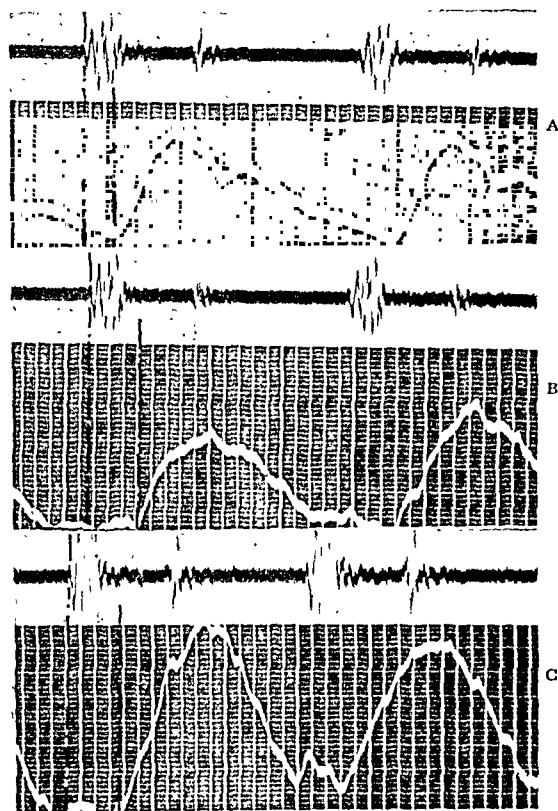


FIG. 5. The arterial wave in the pulmonary circulation in a normal subject. A, pulmonary knob; B, right hilum; C, visible base of the right lung. These tracings have been taken with different degrees of amplification, minimal amplification being used for the pulmonary knob (A) and maximal amplification for the peripheral lung field (C).

veins coming from the middle and lower lobes on the right, in their almost horizontal course, occupy the space between the right heart border and the lower portion of the right hilar shadow thus providing an area mainly occupied by veins. Tracings recorded over this "venous field" present a typical "venous" pattern.³⁵ They show a positive presystolic wave ("a" wave), an early systolic collapse and a gradual rise which culminates at the time of mitral valve opening ("v" wave). (Fig. 4B.)

A satisfactory tracing of the superior vena cava³³ is seldom recorded in normal subjects, young or old. It is more commonly recorded if there is venous engorgement. On the other hand, the tracing of the inferior cava³³ is obtained frequently in deep respiration. It shows a positive wave in presystole, a deep systolic collapse and a

diastolic collapse. It resembles the mechanical tracing of the liver.

Fluorocardiogram of the Child. The infantile fluorocardiogram can be obtained by using the aforementioned filter.⁴² It still presents occasional irregularity or wandering of the base line due to the fact that children frequently have a sudden onset and end of inspiration with an abrupt change in phase. As a result the filter cannot prevent entirely a slight wandering of the base line because the speed of the respiratory wave is similar to that of the cardiac waves. In spite of this, perfectly visible cardiac waves can be obtained over all those cardiovascular and pulmonary structures.

SPECIAL STUDIES OF NORMAL PHYSIOLOGY

Velocity of the Arterial Waves in the Pulmonary Circulation. The velocity of the pulse waves in the lesser circulation has been studied in ten subjects by comparing the tracings obtained by placing the slit first over the pulmonary knob, then over the right hilar shadow and later at the visible base of the right lung.³⁵ (Fig. 5.)

The average times of arrival of the pulse waves are 0.08 second for the pulmonary knob, 0.12 second for the right hilum and 0.16 second for the visible base of the right lung. These data were obtained by measuring the distance on the tracing from the beginning of the first sound to the foot of the wave. Correct figures are about 0.06 second lower because the opening of the pulmonic valves takes place later than the beginning of the sound.

Considering the distances travelled by the pulse wave, the authors calculate a velocity of the pulse waves of 2 M. per second between pulmonary knob and right hilum, and 2.75 M. per second between right hilum and visible base of right lung. While the speed of the pulse in the lesser circulation is less than in the greater, being roughly one-third of the latter, the pulse increases its speed in the small, less extensible arterioles both in the lesser and in the greater circulation.

Temporal Relationship between the Contractions of the Right and Left Heart. Knowledge of the normal temporal relationship of contraction of the two auricles and ventricles is important in various clinical conditions, like bundle branch block, Wolff-Parkinson-White syndrome and interauricular disturbances. Ellinger, Gillick, Boone and Chamberlain^{25,29} found no constant time relationship between the action of the right and left heart in healthy individuals indicating that the right heart may precede the left heart by up to 0.03 second or lag behind 0.01 second.

In order to obtain a double simultaneous tracing two apparatus for fluorocardiography and a "Tri-Beam Stethocardiette" were used. Observations were made on eight normal subjects between the ages of fourteen and forty-six.³⁴ The two ventricles were studied in the left lateral position applying one slit as low as possible across the anterior border of the cardiac shadow (right ventricle) and the other across the lower posterior border (left ventricle). The two auricles were studied with the subject in the right oblique position by applying the slits, one below the right bronchus (left auricle) and the other much lower (right auricle). The pulsations of the pulmonary arch and of the aortic arch were studied with the subjects in the postero-anterior position by applying the slits of the two pick-up units across the borders of the curves corresponding to the two large vessels.

The various observations concerning the temporal relations in cardiac action confirm each other. The final conclusions concerning the time relationship of the ventricular pulsations are based on the correlation of tracings obtained from the auricles (indicating the opening of the A-V valves), from the ventricles (showing the beginning of ejection from both ventricles) and from the large vessels (revealing the initial rise of the aortic and pulmonic pulses). The evidence indicates that the right ventricle contracts first and the interval between the contractions of the two ventricles is between

0.025 and 0.030 second. (Fig. 6). The same interval exists between the pulmonic and aortic pulses. These results indicate an interval which is larger than that found by experimentation on animals. This is partly due to the fact that we measure the intervals between the beginning of ejection of the two ventricles and not between the actual initiation of two systoles.

Observations on the pulsations of the auricles indicate that here, too, there is a brief interval, the right auricle contracting before the left. Our observations, therefore, are consistent with known physiologic facts.

Isometric Relaxation Period of the Left Ventricle. The study of this period is important for both physiologic and clinical studies as it represents the interval between the closure of the aortic valve and the opening of the mitral valve. Several attempts have been made to measure this period in normal subjects by means of arterial and venous tracings or by observation of electrokymograms.²⁸ A phonocardiographic study with simultaneous recording of phonocardiograms and fluorocardiograms led Luisada, Romano and Torre³⁸ to the conclusion that previous figures were too high. Their findings varied between 0.04 and 0.07 second in normal subjects and between 0.07 and 0.11 second in patients with mitral stenosis. They also were able to demonstrate that the small rebound which may be observed occasionally in the tracing of the left ventricle is entirely in the early diastolic phase and starts *after* the opening of the mitral valve.

Attempts at Measurement of Blood Pressure in the Lesser Circulation. In a brief note²² Marchal suggested the use of the fluorocardiogram of the lung (called by him "kinedensigram") for the measurement of blood pressure in the lesser circulation. He tried to reduce the pulsations of the lung by means of an elevation of the intrapulmonary pressure. To this end, he had the patient expire forcibly into a manometer and the complete extinction of the pulmonary pulsation was taken as an indication that the systolic pressure of the pulmonary

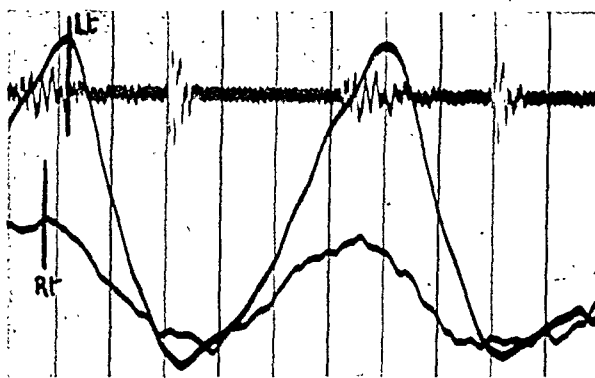


FIG. 6. Simultaneous tracings of the right and left ventricles in the left lateral position. The right ventricle contracts before the left. The upper tracing is a phonocardiogram.

arterioles had been reached by the air of the alveolar cavities. The method, if successful and accurate, would permit the measurement of pressure in the lesser circulation without danger to the patient. Therefore it deserved control. Several series of experiments were performed.

Using a valve which permitted controlled alteration of the positive pressure against which the subject was exhaling, several experiments were performed. High expiratory pressures were followed first by a decrease of the positive pulmonary pulsations, then by their transformation into negative waves.⁴²

The transformation of the tracing, which was followed in some cases by complete disappearance of any pulmonary pulsation, occurred only for pressures of 35 to 50 mm. Hg. As the latter are definitely too high for pulmonary arterial pressures, two possibilities were considered: (1) That the subject may not expire when the pressure of the bottle is higher than that which he can reach. Marchal admitted this possibility. Then the pressure of the manometer does not correspond to that of the respiratory passages. (2) That the pressure of the pulmonary artery is raised temporarily by the increase of the intra-alveolar pressure. In order to check this tests were made on experimental animals.⁴¹ The trachea of an anesthetized dog was connected with the bottle by the valve device already tested in man; the pressure of the right ventricle was

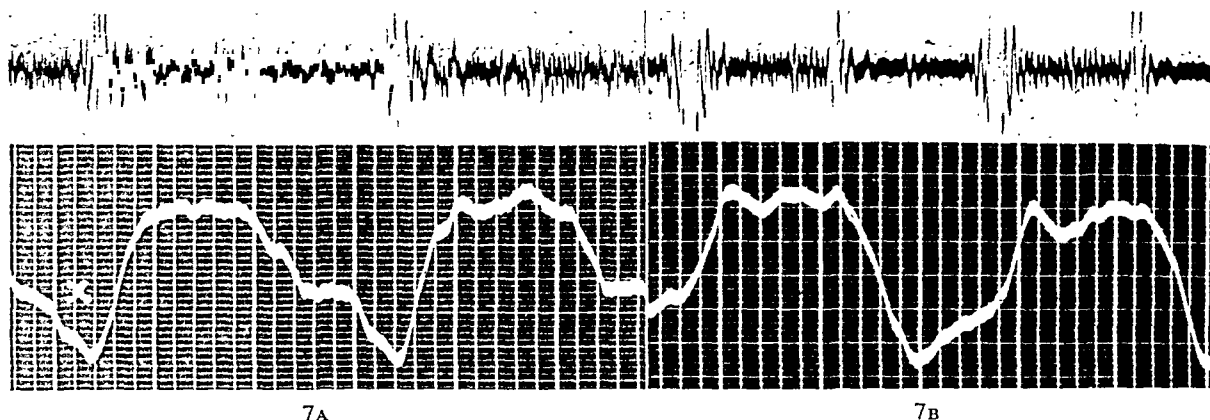


FIG. 7. Tracings of patients with mitral stenosis and insufficiency. A, a patient with sinus rhythm. The negative wave is in presystole (x); the positive plateau is in systole. B, a patient with auricular fibrillation. There is an absent presystolic wave and a positive systolic plateau.

recorded by means of a venous catheter and a Sanborn electromanometer. The ventricular tracing indicates that when the animal expires against pressure, the diastolic pressure of the right ventricle rises becoming positive (increase of residual blood?) and that the systolic pressure rises even further, reaching a level which is over 40 per cent higher than the normal level. This result, in our opinion, invalidates the accuracy of the method for clinical purposes.

OBSERVATIONS IN CLINICAL CONDITIONS

Dynamics of the Left Auricle and Pulmonary Veins in Mitral Valve Lesions. The effects of mitral valve lesions on the left auricle have been studied by numerous authors using different methods (auscultation, inspection and palpation, esophagocardiography). Fairly accurate observations of motion changes of the left auricle have been made in the past by fluoroscopy and roentgenkymography.¹⁷ Fluorocardiographic studies have confirmed and amplified those observations.³⁶ The authors studied twenty-three patients with lesions of the mitral valve. Correlation of the clinical diagnoses, the phonocardiographic findings and the fluorocardiographic tracings led to the following conclusions: (1) In patients with mitral regurgitation or double mitral lesion there is always a positive systolic plateau. (2) In patients with mitral stenosis and no clinical evidence of insufficiency (no systolic murmur) a typical systolic plateau is also

present. (3) The plateau is typical both in cases with sinus rhythm and in those with auricular fibrillation. (Fig. 7.)

The typical pattern in the fluorocardiographic tracing of the left auricle in patients with mitral valvular disease is due to the regurgitation of blood from the left ventricle into the left auricle during ventricular systole. It consists of a rectangular positive "plateau" and resembles both the tracing of intraventricular pressure and that of the left auricle in animals with experimental lesions of the mitral valve.

Another abnormal feature was found in tracings from patients with mitral stenosis and sinus rhythm; this consists of an abnormal form and depth of the auricular wave which was small, irregular and often difficult to visualize. This abnormality may be attributed either to slow emptying of the left auricle because of marked mitral narrowing or to weak left auricular contraction caused by muscle damage in the left auricle.

In conclusion, the fluorocardiogram of the left auricle in mitral valvular disease typically demonstrates a positive plateau (regurgitation during ventricular systole). This is even more pronounced in instances of auricular fibrillation and thus may be of diagnostic value even in the absence of any apical murmur.

In addition, the tracing of the pulmonary veins presents an abnormal and typical pattern in those instances in which the left

auricular tracing shows a plateau. This pattern consists of; (1) high positive auricular wave in presystole if there is sinus rhythm; no auricular wave if there is auricular fibrillation; (2) typical positive plateau in systole similar to that of the left auricle. This proves that the regurgitation of blood from the left ventricle into the left auricle either continues back into the pulmonary veins or causes an increase of pressure and volume in the latter which faithfully reproduces the curve of pressure (and volume) of the left auricle, as was expected theoretically.

Tracings of the Left Ventricle in Myocardial Infarction. The abnormal movements of the left ventricular wall following myocardial infarction have been repeatedly investigated by means of roentgenkymography.^{7,11-17} The most common abnormalities described were diminution or absence of pulsation in a segment of the left ventricular contour, systolic expansion over the lower left contour and diastolic splintering. While most observations were made with the patient in the postero-anterior position, some were made also in the oblique positions.¹²

Luisada and Fleischner³⁷ have studied twenty cases of myocardial infarction. The patients were studied in the sitting position if the lesion was old and in the recumbent position if the lesion was recent. The left ventricle was studied first in the postero-anterior position, then in both obliques (a 40 degree right oblique permits observation of the anterior wall; a 60 degree left oblique, of the posterior wall of the left ventricle). In each of these three positions the study started by applying the slit over the lowest point above the diaphragm or, if the lower profile of the heart was visible through the gastric fundus, over the most medial point of this. Then several different points were studied along the contour of the left ventricle from its lowest to its highest part. The same procedure was repeated in the oblique positions.

Various abnormalities have been observed. Some of them have been found

typical of circumscribed damage to the ventricular wall; others are not specific and may be observed also in cases of diffuse myocardial damage.

Various abnormal patterns were observed during systole. Four of these can be grouped together, being an expression of various

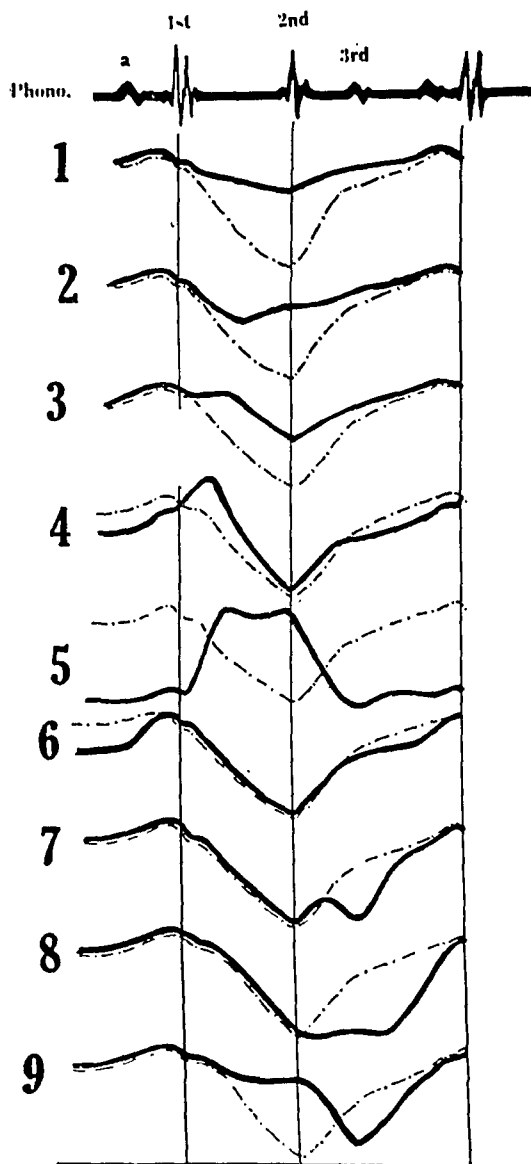


FIG. 8. Scheme of the major abnormalities of the ventricular tracing (continuous line) compared with the normal tracing (dotted line) in myocardial infarction. (1) Decreased amplitude of the ventricular wave; (2) early end of the ventricular wave; (3) late onset of the ventricular wave; (4) early systolic distention followed by normal contraction; (5) systolic distention (dynamic aneurysm); (6) marked presystolic distention; (7) early diastolic rebound; (8) late distention in diastole; (9) decreased amplitude of the systolic wave followed by early diastolic drop.

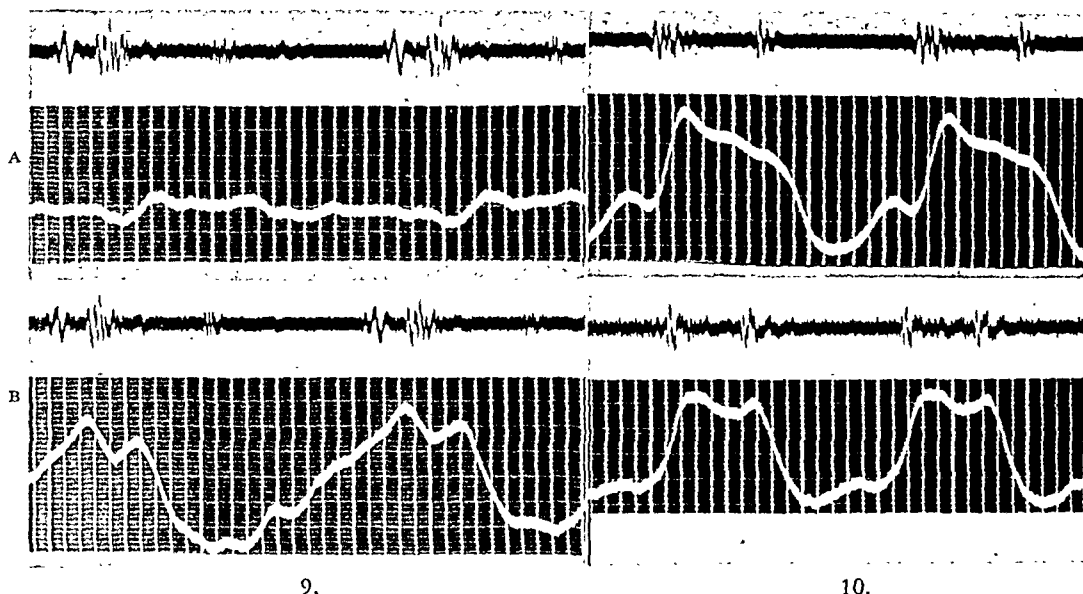


FIG. 9. Tracings of the anterior left ventricular wall in the left oblique position. Old anterior myocardial infarction present. Local paralysis (A) compared with a tracing recorded one step lower (B) which indicates a strong contraction.

FIG. 10. Dynamic aneurysm; inverted or "paradoxical" pulsation with formation of a positive plateau in two cases (A and B) of old myocardial infarction.

degree of the same phenomenon, namely, reduced amplitude, early end or late onset or absence of the ventricular wave. (Figs. 8 and 9.) Two other systolic patterns express a greater or lesser tendency toward distention, namely, early distention followed by normal ventricular wave or inverted pulsation (so-called paradoxical pulsation). (Figs. 8 and 10.) Various abnormal patterns were also observed during diastole, such as a marked rebound, absence of rapid rise or drop of the tracing in early diastole. (Fig. 8.)

In four of the authors' cases the electrocardiogram indicated posterior myocardial infarction; in all of these the abnormality of contraction demonstrated by fluorocardiography was located in the posterior wall and extended to the lateral wall. In eight cases the electrocardiogram indicated anterior or anterolateral myocardial infarction. In six of these the abnormality of contraction was located in the anterior wall and extended to either the apex or the lateral wall; in one case (incompletely studied) a posterolateral abnormality was found; in one no abnormality was observed. In seven cases there was a history of

repeated attacks of myocardial infarction or of attacks of severe, prolonged, precordial pain; in all of them marked abnormalities of contraction were found in the anterior, posterior and lateral wall. There is thus almost 90 per cent agreement between electrocardiogram and fluorocardiogram as to location of myocardial infarctions. (Fig. 11.)

Two abnormalities of the systolic wave have been considered diagnostic of localized myocardial damage, in the majority of instances this being identical with myocardial infarct: (1) Reduced amplitude of the ventricular wave or disappearance of this wave in a circumscribed region of the left ventricle. Whenever the surrounding areas present large waves, this sign is definitely related to infarction. As that area is functionally (and usually also anatomically) excluded from participating in active contraction, the authors suggest the name of local paralysis for the phenomenon thus revealed by fluorocardiography. (2) Inverted pulsation (paradoxical pulsation) of a circumscribed area of the ventricular myocardium. In typical cases this inverted pulsation assumes the aspect of a plateau,

indicating that the inert wall is passively distended by intraventricular pressure. This type of pulsation may be associated with the existence of a well defined bulge of the ventricular silhouette on chest films. In such cases the term ventricular aneurysm

even if taken at the maximum of systole, would show but a minute projection hardly detectable without simultaneous observation of the two opposite motions. The dynamic significance of such an inverted pulsation is similar to that of an aneurysm.

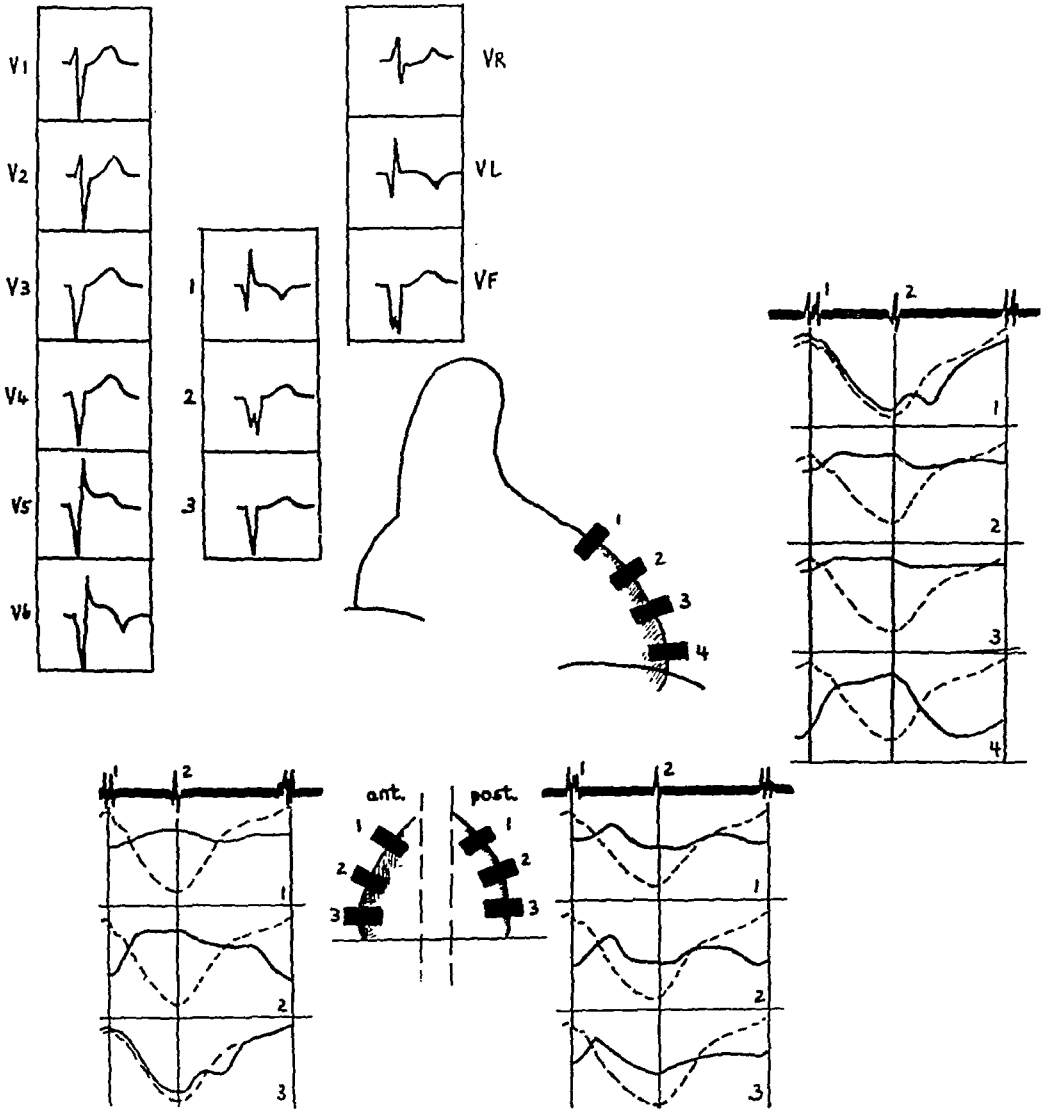


FIG. 11. Diagrammatic locations of the positions of the slit and topographic reconstruction of the morphologic changes in a patient with multiple myocardial infarctions. Dynamic aneurysm extends from the apex to the anterior wall. There is local paralysis above the apex as well as multiple abnormalities of contraction in the posterior wall. There were two older and one recent attack of anterior infarction. Electrocardiograms taken of the limb leads, unipolar chest leads and unipolar limb leads. The schematic tracings on the right side of the figure refer to the fluorocardiograms recorded over the left ventricle in the postero-anterior view (central sketch); those at the bottom refer to tracings recorded over the anterior and posterior wall, respectively, in the oblique positions.

is commonly used. In other cases the bulging occurs only in systole while no bulge is present in diastole. This phenomenon, occasionally observed on fluoroscopy, is hardly noticeable on roentgenograms; these,

The wall distends in systole absorbing part of the dynamic effort of the normal myocardium; it collapses in diastole, disturbing the normal filling and spilling its retained blood into the rest of the ventricular

cavity. This similarity may justify a new term, dynamic aneurysm, for instances in which a typically inverted pulsation is found without any persisting bulge in the profile of the left ventricle.

Both lack of pulsation and inverted pulsation were encountered on either the anterior or the posterior wall, or in one of these locations extending to the lateral wall or in a larger area including anterior, lateral and posterior walls. Most common is either anterior or posterior localization with extension to the lateral wall.

Studies in Uncomplicated Cardiac Shunts. The authors have studied ten such cases between the ages of thirteen and thirty-five. These were all patients presenting characteristic clinical, roentgenologic, electrocardiographic and phonocardiographic findings. Five had a patent ductus arteriosus while the other five had a ventricular septal defect. Speed, shape and height of the pulse waves were studied.⁴² (1) The study revealed a higher speed of the pulmonary arterial wave in the cases of patent ductus; normal or slightly abnormal figures in septal defect. (2) Shape of the pulse waves: This can be studied by measuring the distance foot-peak in the waves. In both groups of patients the pulse was normal (patent ductus) or slightly tardus (septal defect) in the pulmonary knob; it was celer (more so in the patent ductus) in the hilum and pulmonary parenchyma. (3) Height of the pulse waves: In patent ductus arteriosus the pulse wave in the pulmonary knob is frequently as high as or higher than the pulse in the aortic knob. In ventricular septal defect the pulmonic pulsations are higher than the normal but smaller than those of the aorta. The peripheral pulmonic pulses (hilar and parenchymal) are increased in height in both defects but less so in ventricular septal defect.

Even if no typical abnormality was revealed by this study, the diagnosis of the two types of shunts (patent ductus and ventricular septal defect) and the differential diagnosis between them may be made easier by fluorocardiography. More-

over, the finding of a normal left auricular tracing in a patient with a loud systolic murmur is an indirect indication of a septal defect.³⁶

Studies in Chronic Cor Pulmonale. The authors first studied six patients with only mild dyspnea who, despite chronic cor pulmonale, were able to hold their breath during the recording of fluorocardiograms.⁴² In these subjects the pulsation of the pulmonic knob was found greater than in normal subjects and sometimes larger than that of the aortic knob. The pulsation of the hilar shadows was found abnormally high, occasionally as great as that of the pulmonary knob. On the other hand, the pulsation of the pulmonary parenchyma was found abnormally small and, at times, not recordable. In two cases with predominant lesions of one lung the pulsation was imperceptible in that lung but normal in the other. Differences between the various lobes have been observed in cases with lobar predominance of the lesions. These findings reveal a decreased vascularization of the lungs (or part of them) caused by the chronic process and an increased pressure in the larger vessels as a result of the reactive hypertrophy of the right ventricle (pulmonary hypertension and cor pulmonale).

In another patient with severe dyspnea due to emphysema tracings were recorded by using the aforementioned filter.⁴² It was possible to observe the details of the pulsations of the pulmonary artery which had an extremely high dicrotic wave in contrast with the simple profile of the aortic pulse. Also, by means of the filter, it was possible to record a fair pulsation at the base of one lung, no pulsation at that of the other. This coincided with the physical and roentgenologic findings of emphysema which was predominant on one side.

Aortic Aneurysms and Mediastinal Tumors. Differential diagnosis between these two conditions is a problem which frequently confronts the roentgenologist. Both in the case of a mediastinal tumor and in that of an aortic aneurysm the shadow of the mass may pulsate. In the first instance the

pulsation is transmitted; in the second it is due to the expansion of the pouch. While a border fluorocardiogram may not be able to differentiate between the two lesions because in both cases the border will move with a pulsation of arterial type, theoretically a densogram of the shadow would permit easy differentiation. In the case of a tumor the mass is solid and poorly provided with vessels while in the case of an aneurysm the whole mass is full of blood and expands in systole, increasing its thickness.

A study was made in two cases of mediastinal tumors, in two cases of diffuse dilatation of the aorta and in one case of aneurysm of the junction between aortic arch and descending aorta. The tumors gave densograms which revealed only minute, irregular pulsations. The cases with diffuse dilatation and that with the aneurysm gave densograms which are absolutely identical in shape with the border tracings in the same cases and nearly as high. This demonstrates that fluorocardiography may be used for the differential diagnosis between the two conditions. Even in the case of an aneurysm full of clots it is likely that some part of the pouch still communicates with the lumen of the aorta; this should be sufficient to cause an expansive pulsation of the pouch and to give a densogram of arterial type.

Contractions of the Right and Left Auricles in A-V Block. Study of auricular contractions in these conditions requires simultaneous recording of three tracings, the fluorocardiogram, the phonocardiogram and the electrocardiogram. Recording the electrocardiogram while the patient is examined by x-ray requires a special attenuator (or filter) to prevent flickering of the base line. This was previously described by us³¹ and was employed for this particular study. Electrocardiograms also have been taken by others^{20,30} using different technical devices.

The profile of the isolated auricular wave is similar in both the right and the left auricles.⁴² It is much simpler than when the auricular is followed by a ventricular

contraction, on account of the interference of the latter with the auricular volume. The auricular wave consists of a rapid drop followed by a slower rise and closely resembles the profile of a ventricular wave recorded over the border of the left ventricle. This observation is not in full agreement with those of others³⁰ who called a "pure" auricular curve that actually showing very little result of the auricular contraction.

The actual degree of emptying of the auricular chambers can be observed and it is possible to see the influence of ventricular contraction on the subsequent auricular tracings.

MISCELLANEOUS OBSERVATIONS

Arteriovenous Fistula. One such case was studied by recording the tracings of the left ventricular margin. Manual occlusion of the femoral fistula led instantaneously to bradycardia and to a remarkable increase in the amplitude of the ventricular wave; the latter fact was not revealed by either fluoroscopy or serial chest films.

Pericarditis with Effusion. One case was repeatedly studied. During the stage of effusion no visible wave was recorded on any point of the pericardial contour. After paracentesis and introduction of air typical but somewhat small waves were recorded over the left ventricular and right auricular borders above the fluid level. The fluid level itself pulsated and presented a typical ventricular pattern on the left and an auricular pattern on the right. After complete recovery normal tracings were recorded.

Bundle Branch Block. Observations in this field have been made by Ellinger and his co-workers.²⁹

OTHER POSSIBLE APPLICATIONS

This review has been based predominantly on the observations made by one group³¹⁻⁴² since the beginning of their studies about three years ago, although it also covers all other available reports. These early results in the field of physiology and practical clinical application are encouraging. More

is to be expected from continued work and the activity of other groups with this and related methods.

It would seem that the method of fluorocardiography, which is flexible, easy of performance and requires but a small investment in apparatus, deserves wider exploration for its value in pathophysiologic studies and for its clinical usefulness.

SUMMARY

Studies of technic, observations on normal subjects and first clinical applications of a new method are reported. The method permits inscription on a continuous film of either the motions of the border of the cardiovascular silhouette, as observed on the fluoroscopic screen, or the changes in density of the cardiovascular shadows. The method in general is called fluorocardiography; the two types of tracings are termed border tracings and densograms, respectively.

Various tracings and their physiologic interpretations are given in detail.

Studies of cardiovascular physiology are reported; among these are one on the temporal relationship between the contractions of the right and left heart; one on the velocity of the arterial pulse wave in the pulmonary circulation; one on the isometric relaxation period of the left ventricle; and one on pressure recording in the pulmonary artery.

The results of two systematic clinical studies are reported, one in mitral valve lesions, the other in myocardial infarction. In addition, various clinical observations are reported including cases of uncomplicated shunts, cor pulmonale, pericarditis, heart block, aortic aneurysms and others.

REFERENCES

1. GOETT, T. and ROSENTHAL, J. Ueber ein Verfahren zur Darstellung der Herzbewegung mittels Roentgenstrahlen (Roentgenkymographie). *München. med. Wchnschr.*, 59: 2033, 1912.
2. HITZENBERGER, K. and REICH, L. Ein Beitrag zur Roentgenkymographie. *Fortschr. a.d. Geb. d. Roentgenstrahlen*, 31: 17, 1923.
3. STUMPF, P. Das roentgenographische Bewegungsbild und seine Anwendung. Leipzig, 1931, G. Thieme.
4. STUMPF, P., WEBER, H. H. and WALTZ, G. H. Roentgenkymographische Bewegungslehre innerer Organe. *Fortschr. a.d. Geb. d. Roentgenstrahlen*, 47: 241, 1933.
5. ZDANSKY, E. and ELLINGER, E. Roentgenkymographische Untersuchungen am Herzen. *Fortschr. a.d. Geb. d. Roentgenstrahlen*, 47: 648, 1933; 49: 240, 1934.
6. CIGNOLINI, P. Roentgenchimografia Cardiaca e Regmografia. Bologna, 1934. L. Cappelli.
7. PERONA, P. Contributo allo studio della trombosi cardiaca. *Radiol. med.*, 23: 6, 1936.
8. BORDET, E. and FISCHGOLD, H. Radiokymographie du Coeur et des Vaisseaux. Paris. 1937. Masson.
9. HECKMANN, K. Die Grundlagen der Kymographie des Herzens. *Fortschr. a.d. Geb. d. Roentgenstrahlen*, 60: 158, 1939.
10. ROESLER, H. Clinical Roentgenology of the Cardiovascular System. Springfield, 1943. C. C. Thomas.
11. GUBNER, R. and CRAWFORD, J. H. Roentgenkymographic studies in myocardial infarction. *Am. Heart J.*, 18: 8, 1939.
12. GUBNER, R. and CRAWFORD, J. H. Roentgenkymography of the heart. Its clinical application and limitations. *Am. Heart J.*, 18: 729, 1939.
13. SUSSMAN, M. L., DACK, S. and MASTER, A. M. The roentgenkymogram in myocardial infarction. i. The abnormalities in left ventricular contraction. *Am. Heart J.*, 19: 452, 1940. ii. Clinical and electrocardiographic correlation. *Am. Heart J.*, 19: 464, 1940.
14. MASTER, A. M., GUBNER, R., DACK, S. and JAFFE, H. L. The diagnosis of coronary occlusion and myocardial infarction by fluoroscopic examination. *Am. Heart J.*, 20: 475, 1940.
15. GARLAND, L. H. and THOMAS, S. F. Roentgen diagnosis of myocardial infarction. *J. A. M. A.*, 137: 762, 1948.
16. UNGERLEIDER, H. E. and GUBNER, R. Roentgenology of the Heart and Great Vessels. In Stroud's Diagnosis and Treatment of Cardiovascular Disease. Philadelphia, 1945. F. A. Davis.
17. HEIM DE BALZAC, R. and PANNIER, R. La radiokymographie cardio-vasculaire: son utilité et son avenir. *Rev. belge sc. méd.*, 16: 1, 1945.
18. HJELMARE, G. The registration of the movements of the heart with Geiger-Mueller counters and synchronous electrocardiography. *Acta radiol.*, 27: 334, 1946.
19. HECKMANN, K. Moderne Methoden zur Untersuchung der Herz pulsation mittels Roentgenstrahlen. *Ergebn. inn. Med. u. Kinderheilk.*, 55: 319, 1937.
20. LIAN, C. and MINOT, G. La radioelectro-kymographie. *Arch. d. mal. du cœur*, 39: 339, 1946.
21. MARCHAL, M. De l'enregistrement des phénomènes radiologiques invisibles et en particulier des pulsations des artérioles pulmonaires. *Arch. d. mal. du cœur*, 39: 345, 1946.
22. MARCHAL, M. Méthode de mesure de la pression artérielle de l'artère pulmonaire chez l'homme par les rayons X (kinedensigraphie). *Compt. rend. Acad. d. sc.*, 225: 394, 1947.
23. HENNY, G. C. and BOONE, B. R. Electrokymograph for recording heart motion utilizing the roentgenoscope. *Am. J. Roentgenol.*, 54: 217, 1945.

24. HENNY, G. C., BOONE, B. R. and CHAMBERLAIN, W. E. Electrokymograph for recording heart motion, improved type. *Am. J. Roentgenol.*, 57: 409, 1947.
25. CHAMBERLAIN, W. E., BOONE, B. R., ELLINGER, G. F., HENNY, G. C. and OPPENHEIMER, M. J. Asynchronism of ejection of the ventricles as measured with the electrokymogram. *Federation Proc.* 6: 88, 1947.
26. BOONE, B. R., CHAMBERLAIN, W. E., GILICK, F. G. and OPPENHEIMER, M. J. Interpreting the electrokymogram of the heart and great vessel motion. *Am. Heart J.*, 34: 560, 1947.
27. CHAMBERLAIN, E. W. Roentgen electrokymography. *Acta radiol.*, 28: 847, 1947.
28. RANDAK, E. F., ELLINGER, B. R. and OPPENHEIMER, M. J. Ventricular isometric relaxation phase as measured on the electrokymogram. *J. Appl. Phys.*, 1: 534, 1949.
29. ELLINGER, G. F., GILICK, F. G., BOONE, B. R. and CHAMBERLAIN, W. E. Electrokymographic studies of asynchronism of ejection from the ventricles. *Am. Heart J.*, 35: 971, 1948.
30. ANDERSON, T. Electrokymography with simultaneous electrocardiography. *Acta radiol.*, 30: 36, 1948.
31. LUISADA, A. A., FLEISCHNER, F. G. and RAPPAPORT, M. G. Studies in fluorocardiography. New England Heart Association, February 24, 1947.
32. LUISADA, A. A., FLEISCHNER, F. G. and RAPPAPORT, M. B. Fluorocardiography (electrokymography). 1. Technical study. *Am. Heart J.*, 35: 336, 1948.
33. LUISADA, A. A., FLEISCHNER, F. G. and RAPPAPORT, M. B. Fluorocardiography (electrokymography). ii. Observations on normal subjects. *Am. Heart J.*, 35: 348, 1948.
34. LUISADA, A. A. and FLEISCHNER, F. G. The time relationship between the contractions of the right and left sides of the normal human heart. *Proc. Soc. Exper. Biol. & Med.*, 66: 436, 1947.
35. FLEISCHNER, F. G., ROMANO, F. J. and LUISADA, A. A. Studies of fluorocardiography in normal subjects. *Proc. Soc. Exper. Biol. & Med.*, 67: 535, 1948.
36. LUISADA, A. A. and FLEISCHNER, F. G. The dynamics of the left auricle in mitral valve lesions. *Am. J. Med.*, 4: 791, 1948.
37. LUISADA, A. A. and FLEISCHNER, F. G. Tracings of the left ventricle in myocardial infarction. *Acta cardiol.*, 3: 308, 1948.
38. LUISADA, A. A., ROMANO, F. J. and TORRE, J. M. Isometric relaxation period of the left ventricle in normal subjects and patients with mitral stenosis. *Proc. Soc. Exper. Biol. & Med.*, 69: 23, 1948.
39. LUISADA, A. A. La fluorocardiografia. *Cuore e circ.*, 32: 125, 1948.
40. LUISADA, A. A. and FLEISCHNER, F. G. La fluorocardiografia. *Rev. argent. de cardiol.*, 15: 243, 1948.
41. LUISADA, A. A. and FLEISCHNER, F. G. Simultaneous fluorocardiography and intracardiac recording of pressure. *Proc. Soc. Exper. Biol. & Med.*, (in press).
42. LUISADA, A. A. and FLEISCHNER, F. G. Further studies of fluorocardiography. *Am. Heart J.*, (in press).

Seminars on Congestive Failure

Dynamics of Congestive Heart Failure*

DICKINSON W. RICHARDS, JR., M.D.

New York, New York

CONGESTIVE heart failure involves all parts of the heart and circulation. In an analysis of this condition it may be useful to enumerate the main physiologic components of this complex apparatus:

1. Intrathoracic and intra-abdominal great veins and right auricle: the systemic venous reservoir. This contains, in normal conditions, a generous volume of blood under low tension, such that normal stroke volumes of 70 cc. or 80 cc. are removed at each heart cycle, under resting conditions, with only a 3 mm. to 5 mm. change in the right auricular pressure.¹

2. Right ventricle: The volume of blood in the normal right ventricle is not accurately known; it is probably somewhere in the neighborhood of 50 cc. at the end of systole and thus about 130 cc. at the end of diastole.² Systolic right ventricular pressure averages 25 mm. Hg, the end diastolic (filling pressure) 1 to 3 mm. Hg.¹

3. Pulmonary artery: Systolic pressure averages 25 mm. Hg, with a normal range of 18 to 30 mm. Hg, the diastolic pressure is about 8 mm. Hg.

4. Pulmonary capillaries: Pressure in these vessels has been recorded from 7 to 15 mm. Hg.³

5. Pulmonary veins and left auricle: the pulmonary venous reservoir. This is apparently a less voluminous and less distensible blood reservoir than that on the right side as the pressure changes during the cardiac cycle are much wider.⁴ Normally the pulmonary vascular system is thought to contain some 300 to 500 cc. of blood. The mean left auricular pressure is

about 4 mm. Hg higher than that of the right auricle.⁴

6. Left ventricle: There apparently is residual blood in the normal left ventricle at the end of systole,⁵ and the volumes may be presumed to be similar to those in the right ventricle; systolic pressure 120 ± 20 mm. Hg; the end diastolic pressure is probably a few mm. Hg higher than that in the right ventricle.⁴

7. Coronary circulation: There is very little factual information about coronary blood flow in human beings although such studies are now in progress.

8. Systemic aorta, arteries and arterioles: This elastic system, with its systolic pressure of 120 ± 20 mm. Hg and diastolic (in the brachial arteries) around 75 mm. Hg, maintains a flow of blood to tissues throughout the cardiac cycle. There is an extraordinarily effective and sensitive reflex mechanism regulating over-all arteriolar tone, or "peripheral resistance," tending in general to maintain an approximately constant blood pressure in spite of wide changes in cardiac output and in regional blood flows.

9. Systemic capillaries, systemic veins: Here also there are constantly active vasomotor adjustments, both local and regional, in accordance with tissue needs. McMichael,² in his paper in the present series, stated admirably the case for both the existence and the importance of venomotor tone as a factor in cardiocirculatory dynamics.

10. Blood depots, shunts: It is important to realize that there are in the systemic circulation large regional volumes of blood that can be shifted, at need, into the central

* From the Department of Medicine, Columbia University College of Physicians and Surgeons; and the First Medical and Chest Services, Bellevue Hospital, New York, N. Y.

(intrathoracic) venous reservoir and can be maintained there and then shifted away again. The Valsalva experiment results in a large overdilatation of all great veins with blood whether or not the arterial blood pressure falls.⁶ Pericardial tamponade and other central venous obstructions do the same thing, such distention being also sustained. In muscular exercise all visible veins are full of blood while at the same time arteries and arterioles are also dilated. Just where in the periphery this distending blood volume comes from is not clearly known. Krogh's idea⁷ that the splenic-portal-hepatic system is the chief mechanism which shunts blood into the general circulation apparently is true for the dog,⁸ but there is no good evidence that this mechanism operates in man.

The aforementioned is in a sense only an extension of the general notion of venomotor tone, but it is a special aspect of this function and deserves emphasis. Certainly nothing is further from the truth than the oversimplified concept that the circulation consists of an arterial tube and a venous tube, with a resistance between and a pump, the heart, driving fluid around the circuit and that blood volume shifts can only be from arterial tube to venous tube, or *vice versa*.

11. Renal circulation: This controls salt and water balance and thus ultimately tissue and blood volumes. The significance of this function in congestive heart failure has been extensively covered in other papers of this series.^{9,10,30}

Performance of Normal Circulation in Exercise. A knowledge of the action of the normal heart and circulation, especially under conditions of stress, is essential to an understanding of the physiology of congestive heart failure.

In physical exertion of moderate degree, oxygen consumption will be increased from 300 cc. per minute to 1,800 cc. per minute. To provide the tissues with oxygen there will be something like a two-fold increase in arteriovenous oxygen difference and a three-fold increase in cardiac output. The latter is

usually accomplished in part by increase in heart rate and in part by increase in stroke volume.

At this increased level of blood flow, systemic arterial blood pressure normally increases but not greatly; pulmonary arterial pressure is not increased at all;¹¹ indicating in both pulmonary and systemic circuits a marked "compensatory" arteriolar dilatation and decrease in peripheral resistance.

Venous pressures during exercise, or more exactly the effective or "net" filling pressures at the end of diastole in the right and left ventricles, are difficult to ascertain. Earlier studies described increase in peripheral venous pressure, up to about 130 mm. saline, during exercise; more recent work suggests that there may be little rise or even a fall.² The actual "net filling pressure" in the right ventricle, that is, the effective pressure within the thorax, can only be determined by simultaneous measurements of intraventricular and intrathoracic pressures, and this has not been done in exercise in human subjects. Such measurements have been made in a few cases by Lauson et al.⁶ through the respiratory cycle at rest, and by Motley et al.¹² during positive pressure breathing; these measurements indicate that there is, under these conditions at least, a relation between the effective end diastolic filling pressure in the right ventricle and the stroke volume of the ventricle, the stroke volumes changing as much as 25 to 40 per cent for corresponding changes of 2 to 4 mm. Hg in end diastolic pressures. This information is perhaps useful in suggesting that changes in filling pressure in the ventricles need be only very small for considerable increases in stroke volume under certain restricted conditions. How far this can be applied to muscular exercise is unknown.

From the point of view of venous return it is apparent that with the increased cardiac output in exercise, venous blood volumes are shifted so that there is at all times an adequate filling of the central systemic venous reservoir. Heart volume is little if at all increased in normal subjects during moderate

work¹³ and even may be decreased, suggesting that the ventricle increases its stroke volume output by increased emptying rather than increased filling.

Starling's law, on the other hand, states that the energy of cardiac contraction, i.e., stroke volume, is proportional to the diastolic *volume* of blood in the ventricular chamber, up to a certain limiting physiologic volume.^{2,14} Another relationship, often referred to as Starling's law, that the stroke output increases with increasing diastolic filling *pressure* in the ventricle might better be called Frank's law or principle since Otto Frank's extensive experiments¹⁵ with the frog heart led to this general conclusion.

At all events it would seem, as McMichael and others have noted,^{2,16} that the response of the normal heart in moderate exertion does not follow the Starling principle, nor probably the Frank principle either, but operates through other mechanisms, nervous or humoral, tending to increase muscle contractility without increase in fiber length. If there are any increases at all in filling pressure with increased stroke volume, these are very small in magnitude.

When one comes to heavy exertion in normal individuals, however, the situation changes. It has long been recognized that in excessive exercise the heart dilates. Liljestrand, Lysholm and Nylin¹³ found that in heavy work the heart size increased an average of 12.7 per cent. But even here, immediately following the exercise with cardiac output still high, heart volume decreased even below control values. Venous pressures in severe exercise are of course impossible to evaluate as indices of effective intracardiac filling pressures due to unknown changes in mean intrathoracic pressures.

From the aforementioned one may suggest as a general proposition that a dilated heart, with incomplete *emptying* during systole, is a heart under strain. Such dilatation may well induce a further increase in stroke volume, in accordance with the Starling principle, but it is apparently a late response in cardiocirculatory effort.

These observations lead to a consideration of actual cardiac failure of various types.

Failure of Normal Heart under Continued Excessive Strain. A direct and uncomplicated example of this situation is traumatic arteriovenous communication in otherwise normal individuals. This condition can be further analyzed by abruptly shutting off and then releasing the arteriovenous shunt. With a large shunt, the essential findings are as follows:¹⁷ There is a marked increase in cardiac output and a progressive development, over months or years, of cardiac hypertrophy and dilatation. Venous and right auricular pressures are at the upper limits of normal or slightly increased; arterial diastolic pressure is low; blood volumes are within normal limits in most early cases but tend to increase in the more severe cases over a period of years.

Upon abrupt closure of the shunt, heart rate slows; arterial diastolic pressure rises; right auricular pressure shows a small but definite decrease in one series reported^{17a} and no change in another;^{17d} cardiac output is considerably decreased although still above normal. Holman^{17c} has reported a sharp rise in both systolic and diastolic arterial pressures and, in cases with large, long-standing communications and cardiac enlargement, a further dilatation of the heart simultaneous with the blood pressure rise.

It is interesting that a further change reported at this time^{17a} is an increase in blood volume and in local blood flow in the limbs not involved in the shunt. This suggests a regional redistribution of blood away from the central reservoir coincident with decreased cardiac output. Large arteriovenous communications, untreated over many years, may lead to progressive cardiac dilatation, increased blood volume and marked congestive failure.^{17d}

After permanent surgical closure of the shunt rapid diuresis and disappearance of congestive failure occurs; if present, there is also a progressive decrease in heart size to normal over a period of several weeks or longer and a similar gradual return to nor-

mal of the cardiac output. There are obviously various circulatory readjustments in process here.²

From the point of view of the development of heart failure the condition presented by a large arteriovenous communication is important in demonstrating how a sustained increase in cardiac output in a perfectly normal heart may lead first to hypertrophy and dilatation and eventually in some instances to frank congestive failure.

Congestive Heart Failure: "High Output" Forms. There has been considerable difference of opinion and some confusion of thought about this general subject which is certainly not surprising. High output failure includes a variety of very different clinical entities, some of which have not been adequately studied.

Leaving aside the problem of the early stages of development of high output failure about which not much is known as yet and considering only established congestive failure, as for example in severe anemia, one finds the main accepted facts to be that the cardiac output is greatly increased, venous pressures elevated and the congestive state fully established. Blood volumes, as measured by red cell dilution, have been reported as diminished^{18a} but by the plasma dye method, which is probably more reliable, they are usually increased.²⁶

It may well be that from the point of view of tissue needs this increased cardiac output is still inadequate,⁹ but this does not alter the greatly increased burden put upon the heart. Correspondingly, the heart behaves as a heart under strain; the ventricles fail to empty in systole and end diastolic pressures increase although the dilated heart continues to maintain a large output. Whether this state of affairs, before congestion is fully developed, should be called the last stage of "compensation" or the first stage of "congestive failure" is largely academic. As McMichael² puts it, "anemic hearts compensated in this manner are, in fact, on the very brink of failure."

The question has in fact been raised whether the congestive state with large

cardiac output should be called heart failure¹⁹ at all. To this there is the answer, already mentioned,⁹ that the blood flow is still relatively inadequate in these cases, but there is also the much more cogent argument that the congestive state is itself heart failure,¹⁶ a pathologic condition consisting of abnormal intravascular *pressures* rather than deficient intravascular *flow*, but with consequences equally severe—dyspnea, cough, edema, passive congestion of viscera, etc.—all essentially congestive *pressure* phenomena.

Thyroid and beriberi heart disease in congestive failure are similar in mechanics to anemic heart failure. Tissue metabolism in these conditions is greatly disturbed, and the status of the myocardium is also uncertain.

In right-sided congestive heart failure that develops with the pulmonary arterial hypertension of cor pulmonale, high normal or actually increased cardiac output has been found^{20, 21} but the existence of this condition has also been questioned.²² Actually the dynamics of pulmonary heart disease are variable and complex^{1, 23} and patients are encountered with normal or low cardiac output as well as high.

Nonetheless, the high output group constitute a true entity. Marked arterial anoxia is probably important in their causation although there are doubtless other factors. An example, studied recently by Harvey, Ferrer et al.,²⁴ illustrates a number of features that may be encountered in this category. The data are given in Table 1.

The patient, a middle-aged woman with long-standing bronchial asthma, chronic pulmonary emphysema, cor pulmonale and polycythemia, was admitted to the hospital with extreme obstructive dyspnea and in marked right-sided failure. As shown in Table 1 there was marked arterial anoxia, polycythemia, hypervolemia, pulmonary hypertension, right-sided congestion and a cardiac output nearly twice the normal. Digoxin resulted in a small further increase in cardiac output, rise in pulmonary artery systolic pressure and fall in end diastolic right ventricular pressure (i.e., central

venous pressure)—a typical digoxin response in this type of case. The recovery of this patient, however, following use of bronchodilator drugs and repeated phlebotomy was associated with a drop in cardiac output to normal and marked

Additional evidence for this concept was provided by Hickam and Cargill^{11a} who found that cardiac patients actually do fail to increase cardiac output in exercise and furthermore that pulmonary arterial pressures increase further during exercise, sug-

TABLE I

Patient A. D., a female, aged fifty-five.
Diagnosis: Bronchial asthma, pulmonary emphysema, polycythemia, cor pulmonale, congestive heart failure
Residual air—total capacity ratio = 40 per cent

	Arterial O ₂ saturation %	Pressures, mm. Hg			Cardiac Output lit./m.	Index	Blood Volume cc./sq. m.		Hema- tocrit
		Brachial Arterial	Pul- monary Arterial	Right Ven- tricular			Total	Plasma	
Control	60	160/71	64/29	62/11	10.0	6.1	6060	2040	66
86 minutes after digoxin	61	159/75	75/26	75/4	11.6	7.0			
3 wks. later: fully compensated	79	142/79	30/13	30/2	6.0	3.8	3630	1880	48

improvement in arterial oxygen saturation.

To explain this interesting sequence of events it is suggested that the combination of anoxia, polycythemia and hypervolemia was associated with overfilling of the right ventricle, incomplete emptying during systole but a sustained “compensatory” increase in cardiac output, some increase in cardiac emptying with digoxin and decrease in venous congestion. Resolution of the state of congestive failure occurred following relief of anoxia and hypervolemia.

Not all patients, however, respond in this manner. Howarth, McMichael and Sharpey-Schafer²⁰ report some instances in which intravenous digoxin resulted in a decrease in cardiac output.

Congestive Heart Failure: “Low Output” Forms: Intrinsic Myocardial or Valvular Heart Disease. It has long been known that one of the earliest, if not the earliest, of the manifestations of diminished cardiac reserve is the decrease in maximum oxygen consumption that can be achieved during exercise,²⁵ and it has been supposed that this is due to a lack of adequate increase in cardiac output, presumably a left ventricular failure. This occurs in cardiac subjects apparently compensated and with no signs of congestive failure.

gesting additional pulmonary congestion from inadequate left ventricular emptying.

In the course of a progressively diminishing cardiac reserve, in chronic arteriosclerotic or rheumatic heart disease, the point at which resting cardiac output falls below normal probably varies widely from patient to patient; also the point at which frank left-sided congestive failure or right-sided congestive failure makes its appearance is similarly variable. It is certainly true that very low cardiac outputs can exist, especially in the presence of cardiac arrhythmias, in patients at least partially ambulatory with no congestive failure at rest.

Cournand, Ferrer, Harvey and Cathcart²⁶ have recently studied a series of arteriosclerotic or rheumatic subjects with enlarged hearts, but not in the congestive state. Pressures and cardiac outputs were normal. With digoxin the response was that of a normal heart—decrease in cardiac output and no change in venous pressures. This suggests that the heart volume in these patients at rest was optimal for cardiac performance, i.e., not overdilated. How much of the cardiac enlargement was hypertrophy of cardiac walls and how much enlargement of the cardiac chambers could

not be determined. It is possible that with marked cardiac hypertrophy the physiologic intraventricular volume is larger than with normal-sized cardiac muscular walls.

Left Ventricular Failure. Harvey, Ferrer et al.²⁴ have reported a series of five cases of left ventricular failure, the patients being treated with intravenous digoxin. The results are consistent and striking—before administration of the drug cardiac output was very low, pulmonary artery pressures increased, right ventricular end diastolic pressures normal, blood volume normal; after digoxin cardiac output increased, pulmonary arterial pressures fell and right ventricular end diastolic pressures did not change. The effect of digoxin was thus apparently a primary action on the left ventricular myocardium, a more complete emptying of this chamber during systole resulting in an increased cardiac output and decreased pulmonary congestion. There was no evidence in these studies of a peripheral venodilator action of digoxin, as suggested by McMichael and Sharpey-Schafer.²⁷ The data are comparable to some of those reported by Bloomfield et al.²⁸ on the effects of ouabain, except that the latter caused a rise rather than a fall in pulmonary artery pressures.

These data on left ventricular failure are of interest also from the point of view of salt and water balance and development of edema. They were patients chronically in failure, with very low cardiac outputs, and yet who exhibited no tendency to develop edema as the "forward failure" hypothesis of cardiac edema would demand. Studies of the renal circulation in this type of case are obviously indicated and these are in progress.

Combined Right and Left Ventricular Failure: Action of Digitalis. Two series of cases have been reported, by McMichael and Sharpey-Schafer²⁷ and Stead, Warren and Brannon.²⁹

The measurements of the circulation during decompensation were similar in both series, as were the effects of intravenously administered digoxin or lanatoside C. There was a sharp and rapid drop, within ten to twenty minutes, in a previously elevated

right auricular pressure and a large increase in cardiac output taking place within one to two hours. Arterial blood pressure tended to rise, but relatively less than cardiac output, so that the net result was a fall in peripheral resistance. Blood volumes were presumably initially increased in both series although these were not actually measured.

In the studies of Stead et al., following lanatoside C, the same changes also occurred in three patients with severe anemia and increased initial cardiac outputs. The cardiac output increase was found in patients in whom the heart rate showed no significant change as well as in those in whom it was markedly slowed.

McMichael and Sharpey-Schafer noted the similarity of these effects of digoxin to those encountered after venesection, or tourniquets applied to the limbs in patients with congestive failure. They also found that right auricular pressure fell (although only by 1 to 2 cm. saline) in normal subjects given digoxin while at the same time the cardiac output was decreased. The same observations were made in patients with chronic pulmonary disease. They therefore argued that peripheral venous dilatation might be a primary action of digoxin.

The present writer is inclined to hold to a primary myocardial action of digitalis because of the studies of left ventricular failure already mentioned and because of much sound pharmacologic work on the action of digitalis on the heart muscle.

However, whether the response is primary or secondary, the fact remains that with increase in cardiac output associated with digitalization, systemic venous congestion diminishes: there is less blood in the central venous reservoir. As McMichael notes² this blood must go somewhere. The amount that could be accounted for by slight arteriolar dilatation is negligible. On clinical grounds it would seem highly unlikely that the extra blood goes to the lungs because one of the earliest manifestations after digoxin is that the patients can breathe much more easily and, of course, pulmonary arterial pressures decrease. The blood must withdraw, so to speak, into some venous depot when the

cardiac output is increased, perhaps into the muscle depots.

The progressive changes, whether of compensation or decompensation, involving blood volume and total tissue fluids, constitute a further problem.

Origin and Development of Systemic Venous Congestion and Edema. Both the "forward failure" hypothesis and the "backward failure" hypothesis of renal dysfunction in congestive heart failure leading to salt and water retention and edema have been presented in considerable detail in the previous papers of this series^{2,9,10,14,30} and need not be reviewed again. A few clinical considerations may, however, be mentioned.

The association of a tendency toward fluid retention in subjects with impaired heart action is of course axiomatic. This has been established quantitatively by Stead, Merrill and their collaborators^{9,10} in their demonstration of the correlation between decreased renal blood flow and decreased cardiac output. Furthermore, excess body fluid with increased blood volume can by itself induce congestive heart failure. This has been encountered not infrequently in cases of excessive parenteral administration of fluids, for example in postoperative situations. The excess fluid and hypervolemia of water-retention nephritis and the action of desoxycorticosterone probably cause heart failure in large part on these mechanical grounds although arterial hypertension is obviously another factor. The studies of Warren and Stead,³¹ in which administration of salt and water to previously compensated cardiac patients with development of edema before any venous pressure elevation occurred, offer further evidence for the forward failure hypothesis of edema formation.

This hypothesis, however, does not appear to be adequate as the sole explanation for fluid retention in congestive heart failure. It does not explain why patients with low cardiac output with strictly left ventricular failure or those with low cardiac output with no congestion do not retain fluid. It does not explain why diuresis may take place in

recovery from congestive failure, with no increase in renal blood flow or in glomerular filtration rate.³⁰

The venous congestion, or backward failure hypothesis, as a mechanism of fluid retention and edema in congestive heart failure is also valid. That such venous congestion can occur with the failing heart and can be sustained has already been shown. The key to this as a means of water retention has been provided by the experiments of Blake, Wégria, Keating and Ward,³² showing that increased renal vein pressure above 150 mm. saline results in increased tubular sodium and water reabsorption. This would provide an explanation for salt and water retention secondary to venous congestion.

A clinical study demonstrating a primary rise in venous pressure, with developing failure, is that of Reischman and Grant³³ in which withholding of digitalis from previously compensated patients resulted in rise of venous pressure, presumably from inadequate cardiac emptying, before the appearance of weight gain.

It is, of course, true that high venous pressures can exist, as in constrictive pericarditis and other mechanical obstructive conditions, without development of salt and water retention and general edema.

In the present state of knowledge it would seem, as Bradley and Blake have concluded³⁰ that both alterations in renal plasma flow and glomerular filtration and alterations in tubular function may operate in the production of cardiac edema. There may well be other factors, too.

Consequences of Congestive Heart Failure on Peripheral Functions, Pulmonary, Visceral, Etc. These have been well covered by Paine and Smith¹⁴ in their review and by McMichael¹² and need no further emphasis.

CONCLUSIONS

Much has been added to the knowledge of congestive heart failure in recent years, particularly through the measurements of renal function and the measurements made possible by cardiac catheterization.

One of the basic phenomena of congestive

heart failure appears to be inadequate ventricular emptying during systole. The Starling principle, whether or not it applies to the normal heart, does apply to the heart approaching and in failure. At an early stage it is probable that increased ventricular dilatation during systole results in an increased systolic output, the cardiac output thus being maintained to satisfy "tissue needs." Even an increased ventricular diastolic pressure (also requiring increased venous pressure) at times may be a favorable compensation, maintaining cardiac output, as in some cases of anemia.

Such compensation, however, eventually becomes excessive, and the overdilated ventricle passes into the end stage in the Starling curve, with decreased stroke volume and decreasing cardiac output.

The argument is presented that the congestive state as such is a form of heart failure, being failure in terms of intravascular and intracardial pressure rather than in terms of blood flow.

The manner of development and maintenance of the congestive state is variously explained. In left ventricular failure it is probably correct to assume simply that pulmonary congestion is caused in the first instance by failure of emptying of the left ventricle accompanied by adequate systolic output by the right ventricle.

In those forms of incipient failure in which salt and water retention occur early, in accordance with the forward failure hypothesis of Stead and Merrill, right-sided congestion develops secondary to increased blood volume. On the other hand, in the cases in which inadequate right ventricular emptying occurs first, with increased diastolic and venous pressures secondary to this, the congestion appears before the hypervolemia. There is still another group in which cardiac output is low and yet no increase in venous pressure or general congestion is found. Just why the congestive state does develop in one group and not in another is not wholly clear. In most instances anything that can be done to prevent blood from accumulating in venous

reservoirs under high pressure is of advantage to tissues and circulation alike.

Acknowledgments: The editors have kindly made available to the present writer all of the earlier papers of this series, in advance of their publication. In the discussion here offered a connected and logical presentation of the subject has been attempted, rather than any special critique or review of these earlier papers. The latter, however, have been of great assistance and, as will be apparent, have been generously drawn upon. This assistance is hereby acknowledged.

REFERENCES

1. BLOOMFIELD, R. A., LAUSON, H. D., COURNAND, A., BREED, E. S. and RICHARDS, D. W., JR. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardiocirculatory disease. *J. Clin. Investigation*, 25: 639, 1946.
2. McMICHAEL, J. Cardiac venous congestion: its causes and consequences. *Am. J. Med.*, 6: 651, 1949.
3. HELLEMS, H. K., HAYNES, F. W., GOWDEY, J. F. and DEXTER, L. Pulmonary capillary pressure in man. *J. Clin. Investigation*, 27: 540, 1948.
4. COURNAND, A., MOTLEY, H. L., HIMMELSTEIN, A., DRESDALE, D. and BALDWIN, J. Recording of blood pressure from the left auricle and the pulmonary veins in human subjects with interauricular septal defect. *Am. J. Physiol.*, 150: 267, 1947.
5. RICHARDS, D. W., JR., COURNAND, A., MOTLEY, H. L., DRESDALE, D. T. and FERRER, M. I. Relation between electrical and mechanical events of the cardiac cycle in normal and abnormal clinical states. *Tr. A. Am. Physicians*, 60: 65, 1947.
6. LAUSON, H. D., BLOOMFIELD, R. A. and COURNAND, A. The influence of the respiration on the circulation in man, with special reference to pressures in the right auricle, right ventricle, femoral artery and peripheral veins. *Am. J. Med.*, 1: 315, 1946.
7. KROGH, A. *Skandinav. Arch. f. Physiol.*, 27: 227, 1912.
8. BAUER, W., DALE, H. H., POULSSON, L. T. and RICHARDS, D. W., JR. The control of circulation through the liver. *J. Physiol.*, 74: 343, 1932.
9. STEAD, E. A., JR. The role of the cardiac output in the mechanisms of congestive heart failure. *Am. J. Med.*, 6: 232, 1949.
10. MERRILL, A. J. Mechanisms of salt and water retention in heart failure. *Am. J. Med.*, 6: 357, 1949.
- 11a. HICKAM, J. B. and CARGILL, W. H. Pulmonary arterial pressures in congestive failure and emphysema. *Am. J. Med.*, 3: 504, 1947.
- 11b. RILEY, R. L., HIMMELSTEIN, A., MOTLEY, H. L., WEINER, H. M. and COURNAND, A. Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. *Am. J. Physiol.*, 152: 372, 1948.
12. COURNAND, A., MOTLEY, H. L., WERKO, L. and RICHARDS, D. W., JR. Physiological studies of the effects of intermittent positive pressure breathing

- on cardiac output in man. *Am. J. Physiol.*, 152: 162, 1948.
13. LILJESTRAND, G., LYSHOLM, E. and NYLIN, G. The immediate effect of muscular work on the stroke and heart volume in man. *Skandinav. Arch. f. Physiol.*, 80: 265, 1938.
 14. PAINE, R. and SMITH, J. R. The mechanism of heart failure. A resumé of physiologic factors in cardiovascular failure. *Am. J. Med.*, 6: 84, 1949.
 15. FRANK, O. Zur Dynamik des Herzmuskels. *Ztschr. f. Biol.*, 32: 370, 1895.
 16. RICHARDS, D. W., JR. Contributions of right heart catheterization to the physiology of congestive heart failure. *Am. J. Med.*, 3: 434, 1947.
 - 17a. COHEN, S. M., EDHOLM, O. G., HOWARTH, S., McMICHAEL, J. and SHARPEY-SCHAFER, E. P. Cardiac output and peripheral bloodflow in arteriovenous aneurysm. *Clin. Sc.*, 7: 35, 1948.
 - 17b. STEAD, E. A. and WARREN, J. V. Cardiac output in man. *Arch. Int. Med.*, 80: 237, 1947.
 - 17c. ELKIN, D. C. and WARREN, J. V. Arteriovenous fistulas: their effect on the circulation. *J. A. M. A.*, 134: 1524, 1947.
 - 17d. HOLMAN, E. Local and systemic effects of arteriovenous fistulae. *Ann. Surg.*, 112: 840, 1940.
 - 18a. SHARPEY-SCHAFER, E. P. Cardiac output in severe anaemia. *Clin. Sci.*, 5: 125, 1944.
 - 18b. BRANNON, E. S., MERRILL, A. J., WARREN, J. V. and STEAD, E. A., JR. The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. *J. Clin. Investigation*, 24: 332, 1945.
 19. STARR, I. Our changing viewpoint about congestive failure. *Ann. Int. Med.*, 30: 1, 1949.
 20. HOWARTH, S., McMICHAEL, J. and SHARPEY-SCHAFER, E. P. Effects of oxygen, venesection and digitalis in chronic heart failure from disease of the lungs. *Clin. Sc.*, 6: 187, 1947.
 21. RICHARDS, D. W., JR. Cardiac output by the catheterization technique in various clinical conditions. *Federation Proc.*, 4: 215, 1945.
 22. TAGUINI, A. C., FASCILOLO, J. C., SUAREZ, J. R. E. and CHIOLDI, H. Respiration and circulation in pulmonary anoxemia. *Arch. Int. Med.*, 82: 534, 1948.
 23. McMICHAEL, J. Heart failure of pulmonary origin. *Edinburgh M. J.*, 55: 65, 1948.
 24. HARVEY, R. M., FERRER, M. I., CATHCART, R. T., RICHARDS, D. W., JR. and Cournand, A. Some effects of digoxin upon the heart and circulation in man. 1. Digoxin in left ventricular failure. *Am. J. Med.*, in press.
 25. HARRISON, T. L. *Failure of the Circulation*. Baltimore, 1935. Williams and Wilkins Co.
 26. Cournand, A., Ferrer, M. I., Harvey, R. M. and Cathcart, R. T. Unpublished observations.
 27. McMICHAEL, J. and SHARPEY-SCHAFER, E. P. The action of intravenous digoxin in man. *Quart. J. Med.*, 13: 123, 1944.
 28. BLOOMFIELD, R. A., RAPOPORT, B., MILNOR, J. P., LONG, W. K., MEBANE, J. G. and ELLIS, L. B. The effect of ouabain on the dynamics of the circulation in patients with congestive heart failure. *J. Clin. Investigation*, to be published.
 29. STEAD, E. A., JR., WARREN, J. V. and BRANNON, E. S. Effect of lanatoside C on the circulation of patients with congestive failure. A study using catheterization of the right side of the heart. *J. Clin. Investigation*, 81: 282, 1948.
 30. BRADLEY, S. E. and BLAKE, W. D. Pathogenesis of renal dysfunction during congestive heart failure. *Am. J. Med.*, 6: 470, 1949.
 31. WARREN, J. V. and STEAD, E. A., JR. Fluid dynamics in chronic congestive heart failure. *Arch. Int. Med.*, 73: 138, 1944.
 32. BLAKE, W. D., WÉGRÍA, R., KEATING, R. P. and WARD, H. P. The effect of increased renal venous pressure on renal function. *Am. J. Physiol.*, in press.
 33. REISCHMAN, F. and GRANT, H. Some observations on the pathogenesis of edema in cardiac failure. *Am. Heart J.*, 32: 438, 1946.

Clinico-pathologic Conference

Rheumatic Heart Disease with Respiratory Failure*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, N. M., (B. H. No. 163110), was a sixteen year old, white school girl who entered the emergency room of the Barnes Hospital on September 3, 1948, complaining of shortness of breath, fever and general malaise. The family history was non-contributory. The patient was born with a left spastic hemiplegia, presumably due to birth injury, but considerable function returned on the involved side during her lifetime. She apparently had had no significant illness other than that which ultimately led to her admission; no history of any operations was obtained.

At the age of eight the patient had chorea. The episode lasted about six months, and during the next three years there were several recurrences, each of which appeared during the winter months. At the time of the last bout of chorea the patient was admitted to the St. Louis Children's Hospital where her mother was told that the child had rheumatic heart disease. Following discharge she remained well, except for slight shortness of breath on exertion, until eight months before admission when she developed a chill which was followed by fever and cough. She was seen by a private physician and a diagnosis of "flu" was made. Although the acute episode lasted but a short time, the patient never regained her previous state of good health. Weakness, low grade fever, moderate dyspnea on exertion, intermittent aching of the shoulder

and ankle joints without demonstrable signs of inflammation and pain in the muscles occurred to such a degree that the patient was forced to remain home from school. She was confined to bed, however, for only a small portion of the total time that she was ill.

Three months before entry dyspnea increased and the patient was given 0.1 mg. of digoxin daily, with some resultant improvement. Two months prior to admission she developed night sweats, and some weeks later a mild cough productive of a small amount of white mucoid sputum began; concomitantly, the dyspnea grew worse.

Five days before entry the patient had a mild chill, felt feverish, became nauseated and vomited several times. She then apparently felt moderately well until thirty-six hours before entry when she had another chill. Twenty-four hours before admission she became extremely short of breath and complained of rapid pounding of heart. That night she was forced to sit up in bed in order to breathe. Her temperature was 103°F. and she was seen by her physician who prescribed penicillin. She complained of sharp pain in the right chest on deep inspiration, and nausea and vomiting recurred. In addition to digoxin she had apparently received considerable amounts of salicylates until three weeks before her entry to the Barnes Hospital.

At the time of admission her temperature was 39.7°C., pulse 128, respirations 36 and

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

blood pressure 110/70. The patient was a thin, pale girl who was mildly orthopneic. Respirations were rapid and shallow. The skin was hot and dry, but no petechiae were seen and there was no apparent cyanosis. A few slightly tender lymph nodes were present in the anterior cervical, axillary and inguinal regions. These measured $\frac{1}{2}$ to 2 cm. in diameter. The pupils reacted normally to light and accommodation and the optic fundi were normal. Examination of the upper respiratory tract showed mild reddening of the pharynx but no other significant findings. Several teeth were carious. The neck veins were not distended and the thyroid gland was not enlarged. Examination of the lungs revealed them to be resonant to percussion. A few moist rales were present at the right base. Examination of the heart revealed that the left border dullness extended 9 cm. to the left of the mid-sternal line in the fifth interspace. The apex beat was strong and diffuse; a thrill was palpable but because of the extremely rapid rate it could not be timed. The rhythm was regular except for an occasional extrasystole. A loud, harsh, grade iv systolic murmur was heard at the apex and was transmitted toward the sternum. It faded, however, toward the base. There was a low pitched rumble at the apex which could not be accurately timed but which was presumed to be diastolic. A blowing grade ii systolic murmur was heard over the pulmonic area. The pulmonic second sound was accentuated. The abdomen was soft and flat. The liver edge was felt 1 to 2 cm. below the right costal margin and was somewhat tender. The splenic tip was palpable at the costal margin and was soft but quite tender. No costovertebral angle tenderness was elicited. There was slight weakness and spasticity of the left arm and leg, both of which were smaller than the corresponding extremities on the right. The deep tendon reflexes were hyperactive on the left and a questionable Babinski sign was present on that side. There was no edema or evidence of joint inflammation.

The laboratory findings were as follows: Blood count: red cells, 4,200,000; hemoglobin, 12 Gm. per cent; white cells, 20,800; differential count: stab forms, 19 per cent; segmented forms, 63 per cent; monocytes, 18 per cent. Urinalysis: specific gravity, 1.029; albumin, 3+; sugar, negative; centrifuged sediment, several granular casts, 10 to 15 white cells and 1 to 2 red cells per high power field; acetone, 1+; urine culture, no growth. Stool: not obtained. Blood Kahn test: negative. Blood cultures: negative. Throat culture: non-hemolytic *Staphylococcus albus*, non-hemolytic streptococci. Blood chemistry: non-protein nitrogen, 36 mg. per cent; total protein, 5.6 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 2.3 Gm. per cent; chloride, 102 mEq./L.; cephalin-cholesterol flocculation test, 1+; thymol turbidity test, 5 units; venous pressure, 150 mm. of saline; circulation time (decholin), 18 seconds. Electrocardiogram: right axis deviation and sinus tachycardia; abnormal T waves suggestive of auricular enlargement.

On admission to the ward the patient was given oxygen by nasal tube, large doses of penicillin and 0.2 mg. of digitoxin daily. On the evening of the first hospital day a distinct diastolic murmur was heard at the mitral area. The patient's condition was unchanged; rales persisted at the right base and distant wheezing with prolonged expiration was audible over both lung fields. The patient did not produce any sputum. On the following morning her temperature was 38°C., pulse rate 90 and respirations 36 per minute. Inspiratory musical rales were heard over the lower half of both lung fields and a few crepitant rales were also present. Dyspnea was mild and the patient seemed considerably improved. Later that day, however, dyspnea increased. Intravenous aminophylline was injected without beneficial effect, and 0.4 mg. of lanatoside C was given intravenously. Oxygen was administered with a positive pressure mask. Several hours later the patient was again distinctly improved and felt apparently quite well for about one hour. Her temper-

ature then rose to 40.5°C., her pulse rate to 152 and respirations to 50 per minute. Moist crepitant rales and coarse ronchi were heard throughout both lung fields. Tourniquets were applied. Her respirations became more rapid and full-blown pulmonary edema developed. She died shortly thereafter.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: I shall ask Dr. Grunow to present the x-ray findings at this time.

DR. OTTO H. W. GRUNOW: A chest film taken on the day after the patient was admitted to the hospital showed that the heart was globular in contour and somewhat enlarged both to the right and to the left. The aortic arch was inconspicuous. The right auricle was prominent. The left border was rather convex and thus consistent with the diagnosis of mitral valvular disease. The hilar shadows were increased in density and there was increased prominence of markings extending into the parenchyma of the lungs, particularly on the right. The soft hazy infiltration was thought to be compatible with an acute infectious process; the costophrenic angles were clear.

DR. ALEXANDER: This case presents a most interesting problem, and we shall attempt to identify the etiology of the febrile illness which led to this child's death. This patient had chorea on at least three separate occasions, and during the third episode was seen at the Children's Hospital at that time her mother was told that the child had rheumatic heart disease. Presumably then, although none of the other signs of acute rheumatic disease such as arthritis or carditis had been manifest, she did develop heart disease by the age of eleven. Dr. Smith, will you discuss the relationship between chorea and rheumatic fever?

DR. JOHN R. SMITH: It has long been known that chorea is the most common manifestation of rheumatic involvement of the central nervous system and not infrequently, as was the case here, chorea may

occur in the absence of any other symptoms or signs of acute rheumatic fever. In some children chorea is not followed by any permanent cardiac damage whatsoever. I think there is no question, however, that in many cases rheumatic heart disease develops as a sequel to chorea.

DR. ALEXANDER: It is often stated in the literature that chorea is much less apt to be followed by permanent valvular damage than is acute rheumatic fever with polyarthritis. I take it that you do not agree with that statement, Dr. Smith?

DR. SMITH: No, I do not.

DR. EDWARD MASSIE: I believe, as Dr. Smith does, that chorea is very often followed by rheumatic heart disease, probably almost as often as is classical polyarthritic rheumatic fever. It should be pointed out that chorea is more frequent in females than males, the ratio often being given as approximately three to one.

DR. ALEXANDER: Dr. O'Leary, this patient's last episode of chorea occurred at least five years before her death. Do you believe that any demonstrable lesions will be found in the brain?

DR. JAMES L. O'LEARY: The situation here is rather complicated since the patient had a left spastic hemiplegia at birth. On that basis one would expect a reduction in the size of the right internal capsule, probably some diminution in size of the basal ganglia and, as a matter of fact, the entire right hemisphere may be smaller than the left. I doubt that specific choreic lesions would be present five years after the last bout, but it is conceivable that they might be demonstrated.

DR. ALEXANDER: Are the lesions of chorea specific?

DR. O'LEARY: They are said to be pathologically similar in nature to Aschoff nodules. There is some controversy among neuropathologists, however, as to the specificity of the lesion described in chorea.

DR. ALEXANDER: This patient was apparently well for a number of years before her final illness. Although she became ill approximately eight months before entry,

the acute terminal episode began only a few days before admission and was characterized by high fever and severe respiratory symptoms. Dr. Glaser, how do you interpret her clinical course during the last few months of life?

DR. ROBERT J. GLASER: It seems quite clear that this girl had rheumatic heart disease. Further information in regard to the findings during her last few months of life would be most helpful in enabling us to evaluate her course. For example, if we knew how advanced her cardiac disease was the relative importance of cardiac failure could be better estimated. Many of her symptoms prior to entry were suggestive of congestive failure. I think, however, that this patient probably developed acute rheumatic fever—a not unusual occurrence in such a patient as this one—and furthermore, that she not only had carditis but also rheumatic pulmonary involvement. Although rheumatic pneumonitis is not especially common, it seems to be a well described entity.

DR. ALEXANDER: In other words, you believe that this was a “smoldering” rheumatic process which became acute and severe toward the last few days of her life. Are there any other comments?

DR. THOMAS H. HUNTER: I think that Dr. Glaser’s suggestion merits strong consideration, but one of the other possibilities which must be ruled out is that this patient developed subacute bacterial endocarditis eight months before her demise. There are certain features which are compatible with that diagnosis. We are told that she received salicylates for a three-week period, and we also know that she received some penicillin. Although the dosage of salicylates given her is not known, she apparently made no response to them. It is, of course, true that patients with acute rheumatic fever do not always respond to salicylates but, on the other hand, it is conceivable that the lack of response indicated that some other process such as subacute bacterial endocarditis may have been responsible for the illness. The failure to respond well to penicillin does not

constitute strong evidence against the diagnosis of subacute bacterial endocarditis since she probably did not receive adequate amounts of the antibiotic. Against the diagnosis, however, is the absence of obvious embolic phenomena, unless the few red cells in the urine are accepted as evidence of embolization. On the other hand, she had definite renal dysfunction as indicated by the elevated non-protein nitrogen; although azotemia may have arisen on another basis, it is well known that long-standing bacterial endocarditis may lead to significant renal damage. Most patients who have had bacterial endocarditis for eight months would have more marked anemia than did this patient.

DR. ALEXANDER: It should be mentioned that the patient’s spleen was described as tender; that observation is consistent with the diagnosis of bacterial endocarditis.

DR. GLASER: How many blood cultures were obtained?

DR. ERNEST T. ROUSE: Two were taken and both were negative.

DR. ALEXANDER: Are there other diagnoses to be suggested, or shall we consider only the two proposed by Drs. Glaser and Hunter?

DR. W. BARRY WOOD, JR.: I should like to ask Dr. Grunow if the findings in the chest film were compatible with Lutembacher’s syndrome which is characterized by patent foramen ovale and mitral stenosis. It comes to my mind in view of the fact that the x-ray findings suggested a large right auricle and a small aorta. There is no statement as to whether the patient had been fluoroscoped, but fluoroscopy in Lutembacher’s syndrome often reveals the so-called “hilar dance.”

DR. GRUNOW: We had only a postero-anterior film of the chest, and the findings were entirely in keeping with rheumatic valvular disease. I cannot rule out Lutembacher’s syndrome.

DR. ALEXANDER: Dr. Goldman, would you comment on rheumatic pleurisy and rheumatic pneumonitis?

DR. ALFRED GOLDMAN: Rheumatic pleu-

ris is a well accepted manifestation of acute rheumatic fever. I think there is perhaps a bit more controversy in regard to rheumatic pneumonitis since some pathologists apparently are unwilling to accept that diagnosis without qualification. There are many descriptions in the literature of forms of pneumonitis occurring in association with acute rheumatic fever. These vary from lesions in the pulmonary arteries to actual interstitial inflammation in the alveoli. Some of the findings such as edema may be seen in heart failure *per se*, hence the pathologic picture is not always as clearcut as might be desired. I do not believe that Aschoff bodies are actually found frequently in association with acute pneumonitis but they have been described and constitute strong evidence for the entity of rheumatic pneumonia.

DR. WOOD: A recent paper in the Annals of Internal Medicine from the New Haven Hospital described six cases of rheumatic pneumonia which occurred in a series of one hundred patients with acute rheumatic fever.¹ All six of the patients so affected died. The lesions were described in great detail by the pathologists, and I think the most important factor clinically was that the patients all exhibited severe dyspnea and signs of pulmonary involvement without much evidence of congestive heart failure. All had pulmonary involvement at post-mortem examination. I think that the case under discussion today is entirely in keeping with this report, and I agree with Dr. Glaser and Dr. Goldman that the patient probably had acute rheumatic pneumonitis.

DR. MASSIE: This girl had at least two chills and perhaps a third one. I think that finding is described in rheumatic pneumonia. In acute rheumatic fever without pulmonary involvement severe chills are certainly uncommon. In the absence of any evidence of pulmonary involvement the chills would be quite suggestive of subacute bacterial endocarditis but in view of the

evidence of pneumonia they do not help to differentiate between the two diagnoses.

DR. WOOD: Actually many patients with rheumatic heart disease develop secondary bacterial pneumonia as a complication of congestive heart failure, and it is this fact which makes many pathologists reluctant to recognize rheumatic pneumonia as an entity. The question always arises as to whether the pneumonia is secondary to heart failure or is a manifestation of rheumatic fever *per se*. The pneumonic lesions ascribed to rheumatic fever in the article to which I referred seem convincing; further, Dr. Arnold Rich has shown that experimental lesions very similar to those seen in patients with rheumatic pneumonia may arise on the basis of hypersensitivity.²

DR. ALEXANDER: Dr. Massie, what cardiac lesions do you believe will be present?

DR. MASSIE: The answer to your question would be much simpler were this rheumatic heart disease without acute rheumatic fever. It seems likely that the patient had mitral insufficiency and mitral stenosis. It is well known, however, that in acute rheumatic fever with rheumatic carditis, murmurs may appear and disappear in relatively short periods of time; thus the presence of a murmur during acute rheumatic carditis does not necessarily indicate significant permanent valvular damage. Nonetheless, I think that this patient will have mitral stenosis and insufficiency.

DR. ALEXANDER: Do you believe that the patient had cardiac failure?

DR. MASSIE: I am not at all sure that she did; as a matter of fact I favor rheumatic carditis, without failure, and rheumatic pneumonitis as the explanation of the final illness.

DR. ALEXANDER: This patient had marked dyspnea on the night before she came into the hospital and had had some before that. Yet at no time did she have cyanosis or

¹ SELDIN, D. W., KAPLAN, H. S. and BUNTING, H. Rheumatic pneumonia. *Ann. Int. Med.*, 26: 496, 1947.

² RICH, ARNOLD R. and GREGORY, JOHN E. Experimental anaphylactic lesions of the coronary arteries of the "sclerotic" type, commonly associated with rheumatic fever and disseminated lupus erythematosus. *Bull. Johns Hopkins Hosp.*, 81: 312, 1947.

edema and the circulation time and venous pressure were normal. The neck veins were not distended. On the basis of those findings it is rather difficult to make a diagnosis of heart failure, and acute rheumatic carditis may well explain most of her signs and symptoms. If this patient had had rheumatic carditis without pneumonitis, what would you have said of her prognosis, Dr. Massie?

DR. MASSIE: The prognosis of acute fulminating rheumatic fever is bad, particularly when there is marked evidence of carditis. I must repeat that I was impressed by the fact that she had several chills for they suggest to me pulmonary involvement. At the House of the Good Samaritan in Boston I saw a number of young children die with fulminating acute rheumatic fever. Many of these children had very impressive cardiac findings and high fever but no evidence of bacterial invasion of the lungs or blood stream.

DR. GLASER: Even if this patient did have some degree of heart failure her lack of response to the usual measures would have been quite characteristic of a patient with acute rheumatic carditis for it is well known that such patients do not respond to the therapeutic agents which are very effective in heart failure due to uncomplicated rheumatic heart disease.

DR. ALEXANDER: Are patients in this age group likely to die of acute carditis if they do not have severe underlying valvular disease?

DR. MASSIE: The presence of chronic valvular disease has a deleterious influence in the prognosis of acute carditis. I doubt, however, that this girl had severe mitral stenosis.

DR. WOOD: In the cases which were reported from New Haven all of the patients with rheumatic pneumonitis also had acute rheumatic carditis and almost all of them terminally had some degree of heart failure. Apparently the combination of myocardial and pulmonary involvement led to a fatal outcome.

DR. AXEL R. GRONAU: How frequently does one see acute, severe rheumatic

carditis without abnormalities in the electrocardiogram?

DR. MASSIE: I believe the tracing in this case was definitely abnormal in that the T waves were very high and broad, suggesting auricular wall involvement. There was also marked right axis deviation. Some right axis deviation is not unusual at the age of sixteen but in this patient the degree was rather marked. Dr. Gronau probably was more interested in conduction defects, but none was seen here.

DR. CARL G. HARFORD: Did this patient receive penicillin after her admission?

DR. ROUSE: Two blood cultures were taken as soon as she reached the ward, and then penicillin therapy was begun in large dosage.

DR. ALEXANDER: In summary, I believe that we feel that this patient had acute rheumatic fever with acute carditis and probably acute rheumatic pneumonitis as well. Further, she had rheumatic heart disease with mitral stenosis and insufficiency, and she may have had subacute bacterial endocarditis.

DR. WOOD: Dr. Alexander, do you think that this patient had subacute bacterial endocarditis?

DR. ALEXANDER: No, I do not. Do you still think so, Dr. Hunter?

DR. HUNTER: No, I do not really think so, but I don't see how it can be definitely ruled out.

Clinical Diagnoses: Acute rheumatic fever with carditis and pneumonitis; ? subacute bacterial endocarditis.

PATHOLOGIC DISCUSSION

DR. CLARENCE PICKARD: When the chest was opened, the pericardial sac was found to contain 40 cc. of clear yellow fluid. The heart was enlarged, weighing 340 Gm. in contrast to the 180 to 200 Gm. which would be normal for the body weight of this patient. Dilatation and hypertrophy were especially advanced in the right ventricle and in the left atrium. The myocardium of the right ventricle measured 6 mm. in thickness. On the surface of the right atrium

there was a deposit of fibrin 5 cm. in diameter. There was fibrous thickening of the endocardium of the left atrium, the mitral valve and the endocardium of the left ventricle. The tricuspid valve was thickened moderately and on the free edge of one of its leaflets there was a clump of light tan, translucent verrucae $\frac{1}{2}$ to 2 mm. in diameter. The endocardium of the right atrium was slightly thickened. The mitral valve was thickened and fibrotic, and the normal indentations of the commissures of the leaflets were moderately obliterated by fibrous scar tissue. Although the ring measured 75 mm. in circumference, the opening through the valve leaflets was much smaller. A few small fresh verrucae were present on the edges of the mitral valve leaflets. The aortic and pulmonic valves were normal. The myocardium, aside from the hypertrophy, appeared grossly normal.

There were 200 cc. of clear yellow fluid in each pleural space, and a few fibrous adhesions were noted over the upper and lower lobes of the right lung. Small deposits of fibrin were present on the pleural surfaces of each lobe. The lungs were large, firm and of a uniform, rubbery consistency. From their cut surfaces red foamy fluid oozed but there was no profuse bleeding. No focus of bronchopneumonia was apparent.

The other viscera examined were not grossly remarkable.

DR. GUSTAVE J. DAMMIN: From the gross findings several diagnoses were made. The first was that of rheumatic heart disease as evidenced by chronic endocarditis involving the mitral valve with a moderate degree of stenosis. In addition, there were several verrucae on the mitral valve as well as on the tricuspid valve; these indicated an acute, or at least a subacute, rheumatic process. There was fibrinous pericarditis, enlargement of the heart and widespread endocardial thickening, all of which afforded further evidence of chronic and acute involvement of the heart by rheumatic fever.

The second diagnosis concerned the

pulmonary involvement. The lungs exhibited the manifestations of pulmonary edema, but the gross appearance of the lungs was sufficiently different from that of ordinary pulmonary edema to suggest that this was an instance of rheumatic pneumonia, and that diagnosis was made on the basis of the gross specimen. It is difficult to define the gross characteristics of rheumatic pneumonitis and to differentiate it from the changes of subacute passive congestion. In this specimen the interstitial tissue was thickened, there was some fluid in the alveoli and the light color was more suggestive of pneumonia than is the darker color which one associates with chronic passive congestion. There also was fibrinous pleurisy and in each pleural cavity fluid was present.

The first section (Fig. 1) is from the myocardium at the base of the left ventricle and shows an Aschoff nodule which has the fusiform shape associated with such nodules at the end of one or two months. Some of the cells within the nodule have very dense nucleoli and can be identified as Anitschkow cells. An outstanding and characteristic feature of these cells is the basophilic, rod-shaped nucleus which extends the entire length of the cell; the Anitschkow myocyte is the reticulum cell of the myocardium. It is believed by many that Anitschkow cells are the precursors of the Aschoff cells which form rheumatic nodules in the myocardium.

Figure 2 is a photograph of a portion of the tricuspid valve. There is prominent vegetation, the outer surface of which is composed entirely of fibrin; a few fibroblasts are present at the base of the vegetation. These features constitute evidence of acute verrucous endocarditis of rheumatic origin. Just beneath the vegetation the valve structure is acellular and fibrous, indicating a chronic inflammatory process in the valve. In the base of the mitral valve (Fig. 3) there is an abnormal number of large vessels which indicate previous inflammatory involvement; the valve has been thickened by a large amount of hyalinized collagen.

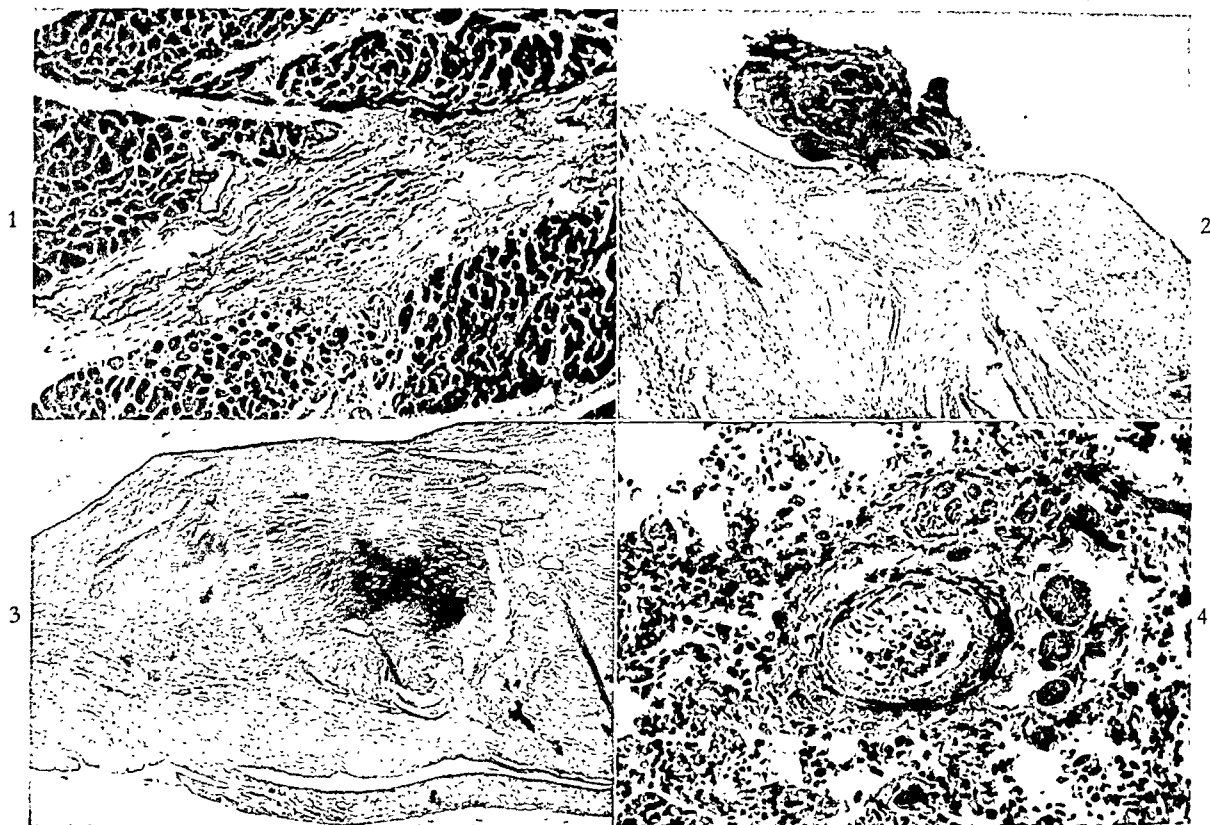


FIG. 1. Aschoff nodule of one to two months in age in the myocardium at the base of the left ventricle.

FIG. 2. Acute verruca on the scarred leaflet of the tricuspid valve.

FIG. 3. Dense collagenous scarring and thickening of a leaflet of the mitral valve with prominent vascularization, particularly on the right side of the field.

FIG. 4. Intimal thickening of rheumatic arteritis in a small pulmonary vessel.

In sections of the lungs there were anatomic changes, the appearance of which did not permit exact separation on an etiologic basis. Some of the smaller arteries of the lungs were thickened, primarily in the media, as occurs in pulmonary hypertension. Other vessels showed the change illustrated in Figure 4—proliferation of the intima without change in the media. This change is one of the more characteristic ones found when there is rheumatic involvement of the arteries, regardless of their location. It has been described in the vessels of the liver, pancreas, heart and lungs. In this section macrophages are also seen. Although it is not apparent in the photomicrograph many of the macrophages contain large amounts of hemosiderin, evidence of some degree of chronic passive congestion. There is also some interstitial thickening and increased cellularity of the alveolar walls. These features are more

apparent in a less highly magnified photomicrograph of the lung (Fig. 5) where there is shown infiltration of both polymorphonuclear and mononuclear cells in the alveolar walls; fibrin is also seen in and along the walls of some of the alveoli. In the fibrin there are a few polymorphonuclear leukocytes. These findings are indicative of rheumatic pneumonia. We did not find the great number of hyaline thrombi which are commonly associated with rheumatic pneumonia, nor did we see any foci in the alveolar walls of specific fibrinoid nodules which are described in this disease. There were, however, many hemorrhages into the alveoli, a common finding in rheumatic pneumonia. The total picture was interpreted as representing the changes of both chronic passive congestion and of acute rheumatic pneumonitis.

Microscopic examination of the liver revealed a lesion which was entirely un-

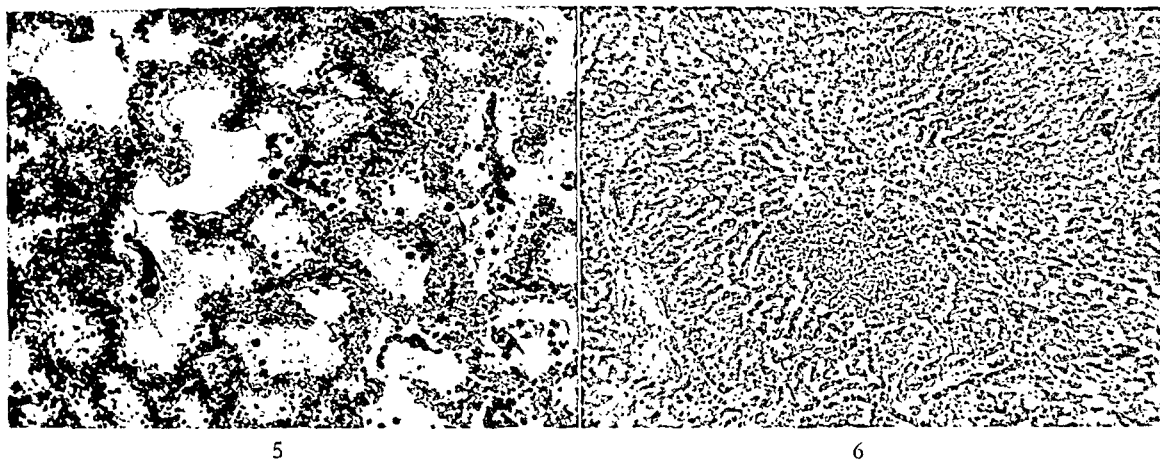


FIG. 5. Thickened and infiltrated alveolar walls and precipitated protein, fibrin and macrophages within the alveoli. The varied character of these changes indicates the combined effect of both congestion and rheumatic pneumonitis.

FIG. 6. Section of the liver showing mid-zone necrosis.

expected from the gross appearance of the organ. In almost every hepatic lobule there was an area of necrosis, most often found in the mid-zone of the lobule. This finding is illustrated in Figure 6. Such necrosis is not the type that occurs usually with acute passive congestion for it was removed from the portal and central veins. In fact, the congestion of the abdominal viscera was minimal. There are few references to changes in the liver in rheumatic fever. In May Wilson's monograph on rheumatic fever, however, she refers to similar mid-zone necrosis which she noted in a very few of her cases.³

To summarize our findings then, there were the manifestations of chronic rheumatic endocarditis with involvement of the endocardium and the myocardium, and of acute rheumatic carditis with involvement of the valves, the presence of Aschoff nodules in the myocardium and the presence of fibrinous exudate and fluid in the pleural cavities.

There definitely were two distinct processes in the lungs, and the degree to which each change contributed to the final picture cannot be accurately determined. Chronic passive congestion of the lungs was present although the terminal heart failure was

primarily that of the left heart; there was no fluid in the peritoneal cavity nor did any of the abdominal viscera show a significant degree of passive congestion. The passive congestion in the lungs was probably of short duration, but there was also pneumonitis characterized by the presence of fibrin in the alveoli and interstitial infiltration of the alveolar walls by mononuclear and polynuclear cells. The vessels in the lungs showed changes which were compatible both with pulmonary hypertension of some standing and with rheumatic arteritis. Actually the rheumatic arteritis was healed for the change was primarily that of intimal thickening in the smaller arteries.

The changes in the liver were rather unusual; as indicated there is only one reference in the literature to such changes. It is interesting that the thymol turbidity and the cephalin-cholesterol tests were normal.

The brain was not examined.

Anatomic Diagnoses: Chronic endocarditis of the mitral valve with moderate stenosis; acute verrucous endocarditis of the mitral and tricuspid valves; chronic and subacute rheumatic myocarditis; chronic passive congestion and edema of the lungs, moderate; acute interstitial pneumonitis involving all lobes of the lungs; focal necroses in the liver, primarily mid-zonal.

³ WILSON, M. G. *Rheumatic Fever*. New York, 1940. Commonwealth Fund.

Gastric Alkalosis with Hypokalemia*

THOMAS J. KENNEDY, JR., M.D., JOHN H. WINKLEY, M.D. and MARCELLE F. DUNNING, M.D.
New York, New York

ALKALOSIS caused either by loss of gastrointestinal secretions or by excessive intake of alkali occurs frequently and the outstanding clinical and laboratory features of the syndrome have been thoroughly described.¹⁻¹⁸ Within the last few years reduction of the serum potassium concentration has been observed as an occasional feature of alkalosis in some cases due to Cushing's syndrome,^{19,20} congenital alkalosis with diarrhea²¹ and gastric alkalosis.^{22,23} In most of these instances the electrolyte composition of serum is abnormal in that the (K^+) and (Cl^-) are reduced while the (HCO_3^-) is elevated.

The major portion of the potassium content of the body is contained not in the extracellular but in the intracellular fluid, about 70 per cent of which is muscle fluid. In each of the aforementioned clinical syndromes evidence indicating loss of intracellular potassium has been presented. Muscle cells in one case of Cushing's syndrome with alkalosis²⁴ and in two cases of gastric alkalosis²⁵ have been shown to contain abnormally low concentrations of potassium and abnormally high concentrations of sodium. Balance studies^{20,21,23,25,26} have indicated that in the intracellular fluid (K^+) was low and that potassium was replaced by sodium.

Potassium depletion in the rat, produced experimentally by low potassium diets (cf. congenital alkalosis with diarrhea and gastric alkalosis) and/or administration of large doses of desoxycorticosterone acetate (cf. Cushing's syndrome), has resulted in the

development of an electrolyte disturbance characterized by alkalosis, elevation of serum (HCO_3^-), reduction of serum and muscle (K^+) and elevation of muscle (Na^+).²⁷

The therapeutic implications of these disturbances in electrolyte composition of body fluids are important. In congenital alkalosis with diarrhea²⁸ and in Cushing's syndrome with hypokalemia and alkalosis^{19,20} use of potassium salts has been shown to be beneficial. The observation has been made that repair of the disturbance is not possible by administration of sodium or ammonium salts unless potassium salts are also employed.

The case herein reported is one of gastric alkalosis in an adult with evidence of potassium deficiency treated successfully with potassium chloride in addition to sodium and ammonium chloride.

CASE REPORT

A forty-nine year old white male cabinet worker was admitted to this hospital with the chief complaints of weakness, anorexia, diarrhea, weight loss and swelling of the extremities. Fourteen years before admission a posterior gastroenterostomy had been performed for epigastric pain. He was asymptomatic thereafter until seven months before admission when the symptoms which brought him to the hospital appeared and became progressively worse. Work-up revealed clinical and laboratory evidence of malnutrition; a gastrojejunocolic fistula was demonstrated roentgenographically. Every effort was made to improve the patient's nutritional status preoperatively. His diarrhea

* From the First (Columbia) and Third (New York University) Research Services and the Third (New York University) Surgical Division, Goldwater Memorial Hospital, New York, N. Y. and The Department of Medicine, College of Physicians and Surgeons, Columbia University and the Departments of Medicine and Surgery, College of Medicine, New York University, New York, N. Y.

was brought under control and he regained 15 of the 45 pounds which he had lost. Three months after admission the fistulous tract was excised *en bloc*, intestinal continuity was reestablished and a temporary cecostomy was done. Postoperatively there was only moderate drain-

TABLE I

SUMMARY OF AVAILABLE DATA ON FLUID AND ELECTROLYTE BALANCE DURING IMMEDIATE POSTOPERATIVE PERIOD

Post-operative Day	Intake			Output	
	Parenteral Fluids cc./day*	Oral Fluids cc./day†	Sodium Chloride mEq./day	Wangensteen Drainage cc./day	Urine cc./day
0	3,000	350	2,400	Unrecorded
1	4,000	170	3,000	Unrecorded
2	6,500	380	4,000	1,125
3	5,000	340	4,800	900
4	3,000	1,260	280	4,200	550
5	4,000	4,500	415	2,100	1,100
6	6,000	2,060	555	2,050
7	2,000	3,560	280	1,850
8	3,600	150	1,900

* Includes whole blood, plasma, saline, dextrose in saline, dextrose in distilled water and amigen.

† Includes milk, fruit juice and water.

age (about 250 cc. per day) from the cecostomy tube. However, drainage from the intragastric suction ranged from 2 to 5 liters per day. (Table I.) Parenteral replacement therapy is listed in Table I. Apathy and drowsiness appeared and increased progressively from the second postoperative day, and by the sixth day most of the classical clinical and laboratory signs of alkalosis were present.

Chemical determinations reported herein were performed by methods conventionally used in the study of acid-base disturbances. Heparinized arterial blood was collected and handled anaerobically for all determinations. Values for (HCO_3^-) were calculated from the measured pH and total CO_2 content. Sodium and potassium were determined flame-photometrically. Concentration of sodium (or potassium) per liter of erythrocytes, (Na^+)_e was calculated from whole blood, (Na^+)_{w.b.} and plasma (Na^+)_p sodium concentrations by the formula:

$$(\text{Na}^+)_e = \frac{(\text{Na}^+)_{w.b.} - (\text{Na}^+)_p(1 - \text{Hematocrit})}{\text{Hematocrit}}$$

As can be seen from Table II the alkalosis initially was very severe and associated with high plasma (HCO_3^-) and low plasma (K^+). There was a striking deficit in erythrocyte (K^+) counterbalanced by an increased (Na^+).

The P_{CO_2} calculated from the data was 60 mm. Hg, quite in keeping with the patient's slow, shallow respiration. Electrocardiogram showed a prolonged Q-T interval. Renal function studies performed at the height of the alkalosis (Table III) showed reduction in filtration rate. Despite this and the reduction of plasma (K^+) the excretion rate of (K^+) was high (about 50 mEq./day). Notwithstanding the severe alkalosis and greatly elevated plasma (HCO_3^-), the urine was unequivocally acid.

When the nature and extent of the disturbance of the electrolyte structure of the patient's body fluids was appreciated, intragastric suction was discontinued. Therapy with intravenous potassium chloride was started. The first 7.5 Gm. induced only a slight but significant rise in the plasma (K^+), associated clinically with improvement in the patient's state of consciousness. In the next thirty-six hours the patient received 10 Gm. of potassium chloride orally and 24 Gm. of ammonium chloride. On this regimen there was prompt clinical improvement and rapid reversion of the laboratory findings to normal. (Table II.) Physiologically correct concentrations of potassium and bicarbonate in plasma and of potassium and sodium in erythrocytes were restored seventy-two hours after the beginning of therapy. The patient's subsequent course, without further therapy, was uneventful.

COMMENTS

Depletion of the total body K^+ , a feature of gastric alkalosis which has heretofore not been emphasized in the adult, was assumed to exist in this case on the basis of low plasma and erythrocyte (K^+). Darrow²⁷ has shown that in the rat a reciprocal relationship exists between the (Na^+) and (K^+) of muscle cells and that the latter varies inversely with the serum (HCO_3^-). While the data on erythrocyte cation composition, as computed by difference, are liable to large errors and are less useful than when in terms of concentration in cell water, the conclusion is probably valid that erythrocyte K^+ had been replaced by Na^+ at the height of the alkalosis. When the (HCO_3^-) returned to normal, the erythrocyte (K^+) was restored. The relationship, therefore, between erythrocyte (Na^+) and (K^+) and

plasma (HCO_3^-) in this patient was comparable to that observed by Darrow in rat muscle and serum.

The depletion of body potassium in an individual whose intake was essentially zero probably resulted from a combination of

severe metabolic alkalosis has been reported previously.³¹ We have not remeasured this patient's inulin clearance. However, the variation in blood urea nitrogen levels rising from normal preoperatively to 45 mg. per cent on the fifth postoperative day, to

TABLE II
SUMMARY OF DATA ON BLOOD ELECTROLYTE COMPOSITION*

Post-operative		Plasma							Erythrocyte†	
Day	Time	pH	Na ⁺ mEq./L.	K ⁺ mEq./L.	Cl ⁻ mEq./L.	Total CO ₂ mM./L.	HCO ₃ ⁻ mEq./L.	Hemato- crit Per Cent	Na ⁺ mEq./L.	K ⁺ mEq./L.
6	9 P.M.	7.59	138	1.71	68	56.6	54.8	40	45	69
7	10 A.M.	7.55	138	2.04	...	56.1	54.1			
8	10 A.M.	136	3.46	94	34.1				
10	10 A.M.	7.46	137	3.67	100	27.1	25.9	40	5	96

* Between 1 A.M. and 10 A.M. on the seventh postoperative day the patient received 7.5 Gm. of KCl parenterally.
† Expressed as per liter of erythrocytes.

TABLE III
SUMMARY OF RENAL FUNCTION STUDIES

Total Concurrent Time	Plasma K ⁺	Urine Flow	Inulin Clearance	Excreted			Urine pH
				K ⁺	NH ₄ ⁺	Titratable Acid	
Minutes	mEq./L.	ml./min.	ml./min.	μEq./min.	μEq./min.	μEq./min.	
-60		Infusion started containing NaCl 143 mEq./L. at 6 ml./min.					
0-17	1.80	2.00	75	39	34	15	5.90
17-39	1.82	2.00	78	36	34	16	6.09
39-56*	1.78	1.71	66	26	35	15	6.00
56		Infusion changed to NaCl 130 mEq./L. KCL 50 mEq./L. at 6 ml./min.					
121-142	2.01	1.57	76	27	35	14	6.14
142-163*	2.09	1.43	66	19	28	13	6.10

* The data suggest that urine collections in these two periods were incomplete.

loss of gastrointestinal secretions (containing an average of 7 mEq. /L. of K⁺)* and failure of the kidney to retain this ion in the face of severe depletion. The long antecedent period of diarrhea may have been a contributing factor as in the sprue syndrome.^{29,30}

The inulin clearance was somewhat low. Temporary depression of filtration rate in

* While this figure represents an average from the literature, it is noteworthy that gastric secretions have concentrations of K⁺ averaging about 20 mEq./L. and ranging up to 30 mEq./L.⁴⁸⁻⁵⁰

55 mg. per cent on the sixth and back to 28 mg. per cent on the seventh suggests that the observed azotemia was attributable, in part, to an acute depression of filtration rate.

More serious renal damage manifested by prolonged elevation of the blood urea nitrogen, hypertension, marked oliguria or anuria, hematuria, proteinuria and cylindruria have been frequently reported in association with the metabolic alkalosis induced by loss of gastrointestinal secretions

or by excessive intake of alkalis.^{1-5,9-18,32-35} While in some instances pre-existing renal damage was known to have been present, in others renal function was quite normal before the episode of alkalosis. The damage usually proved reversible. In those patients who succumbed during alkalosis histopathologic examination revealed lesions which were located predominantly in the tubular epithelium.^{2,11,33,37} The latest available necropsy protocol points out that the lesion is situated in the ascending portion of the distal convoluted tubule and bears a striking similarity to the picture occurring in the "crush" syndrome ("lower nephron nephrosis").³⁸

The excretion of an acid urine by a patient with severe alkalosis is surprising. This observation has been made and commented upon in previous reports.^{3,16,26,34,39} It has been noted in dogs⁴⁰ and in normal men^{40a} that in alkalosis induced by administration of sodium bicarbonate the urine pH became alkaline whenever the plasma (HCO_3^-) exceeded 25 mM./L. While no measurements of urinary CO_2 content were made in this patient, no more than a trace could have been present at the observed urinary pH. Yet this patient's plasma (HCO_3^-) was in excess of 50 mM./L. Patients with nephritis require more alkali and higher plasma (HCO_3^-) to achieve an alkaline urine.⁴¹⁻⁴⁴ The electrocardiograms taken showed no abnormalities except prolongation of the Q-T interval. Such prolongation is frequently observed in hypokalemia.⁴⁵

From a therapeutic standpoint it seems obvious that potassium salts should be administered to adults with alkalosis when potassium depletion is also present. If oral administration is impractical, they may be given intravenously (in concentrations under 75 mEq./L. to avoid local pain) or by hypodermoclysis. The electrocardiogram is a valuable tool to indicate impending toxicity from overmedication with potassium salts due to its distinctive pattern in hyperkalemia. Several recent papers have

reviewed the distinctive electrocardiographic patterns.⁴⁵⁻⁴⁷

SUMMARY AND CONCLUSIONS

A case of severe metabolic alkalosis is presented. Unusual findings to which attention is called include a reduction of plasma (K^+); reduction of (K^+) and elevation of (Na^+) of erythrocytes; urinary pH of 6.0 when the blood pH was 7.59, and reduction of glomerular filtration rate (inulin clearance). Therapy with potassium and ammonium chloride was followed by prompt clinical improvement and by rapid restoration to a normal plasma and erythrocyte electrolyte pattern.

Acknowledgment: The authors gratefully acknowledge the helpful advice and criticism given them by Dr. Robert W. Berliner.

REFERENCES

1. HARDT, L. L. and RIVERS, A. B. Toxic manifestations following alkaline treatment of peptic ulcer. *Arch. Int. Med.*, 31: 171, 1923.
2. BROWN, G. E., EUSTERMANN, G. B., HARTMAN, H. R. and ROWNTREE, L. G. Toxic nephritis in pyloric and duodenal obstruction. *Arch. Int. Med.*, 32: 425, 1923.
3. ELLIS, A. W. M. Disturbance of the acid base equilibrium to the alkaline side. *Quart. J. Med.*, 17: 405, 1923-1924.
4. GATEWOOD, L. C. The dangers and the essential safeguards in the alkali treatment of peptic ulcer. *Illinois M. J.*, 48: 491, 1925.
5. HOUGHTON, L. W. Three cases of toxemia following obstruction near the pylorus. *Guy's Hosp. Rep.*, 75: 149, 1925.
6. JORDAN, S. M. Calcium, chloride and carbon dioxide content of venous blood in cases of gastro-duodenal ulcer treated with alkalis. *J. A. M. A.*, 87: 1906, 1926.
7. GATEWOOD, W. E., GAHLER, O. H., MUNTWYLER, E. and MYERS, V. C. Alkalosis in patients with peptic ulcer. *Arch. Int. Med.*, 42: 79, 1928.
8. WILDMAN, H. A. Chloride metabolism and alkalosis in the alkali treatment of peptic ulcer. *Arch. Int. Med.*, 43: 615, 1929.
9. COOKE, A. M. Alkalosis occurring in the alkaline treatment of peptic ulcer. *Quart. J. Med.*, 1: 527, 1932.
10. WILKINSON, S. A. and JORDAN, S. M. The significance of alkalosis in the treatment of peptic ulcer. *Am. J. Digest. Dis.*, 1: 509, 1934.
11. RYLE, J. A. Prostatic and gastric uremia. *Lancet*, 1: 198, 1935.
12. OAKLEY, W. M. Alkalosis arising in the treatment of peptic ulcer. *Lancet*, 2: 187, 1935.
13. BERGER, E. H. and BINGER, M. V. The status of the kidneys in alkalosis. *J. A. M. A.*, 104: 1383, 1935.

14. JEGHERS, H. L. and LERNER, H. H. The syndrome of alkalosis complicating the treatment of peptic ulcer. *New England J. Med.*, 214: 1236, 1936.
15. EISELE, C. W. Changes in the acid base balance during the alkali treatment for peptic ulcer. *Arch. Int. Med.*, 63: 1048, 1939.
16. NICOL, B. M. The renal changes in alkalosis. *Quart. J. Med.*, 9: 91, 1940.
17. KIRSNER, J. B. and PALMER, W. L. Alkalosis complicating the Sippy treatment of peptic ulcer. *Arch. Int. Med.*, 69: 789, 1942.
18. GRACE, W. J. and BARR, D. P. Complications of alkalosis. *Am. J. Med.*, 4: 331, 1948.
19. MCQUARRIE, I., JOHNSON, R. M. and ZIEGLER, M. R. Plasma electrolyte disturbance in a patient with hypercorticoadrenal syndrome contrasted with that found in Addison's disease. *Endocrinology*, 21: 762, 1937.
20. WILLSON, D. M., POWER, M. H. and KEPLER, E. J. Alkalosis and low plasma potassium in a case of Cushing's syndrome: metabolic study. *J. Clin. Investigation*, 19: 701, 1940.
21. DARROW, D. C. Congenital alkalosis with diarrhea. *J. Pediat.*, 26: 519, 1945.
22. ALLOTT, E. N. and MCARDLE, B. Further observations on familial periodic paralysis. *Clin. Sc.*, 3: 229, 1938.
23. MUDGE, G. H. Muscle electrolytes in patients with potassium depletion. *J. Clin. Investigation*, 27: 550, 1948.
24. POWER, M. H.²⁷
25. DARROW, D. C. The retention of electrolyte during recovery from severe dehydration due to diarrhea. *J. Pediat.*, 28: 515, 1946.
26. GAMBLE, J. L., FAHEY, K. R., APPLETON, J. and MACLACHLAN, E. Congenital alkalosis with diarrhea. *J. Pediat.*, 26: 509, 1945.
27. DARROW, D. C., SCHWARTZ, R., IANNUCCI, J. F. and COVILLE, F. The relationship of the serum bicarbonate concentration to muscle composition. *J. Clin. Investigation*, 27: 198, 1948.
28. GOVAN, C. D. and DARROW, D. C. The use of potassium chloride in the treatment of dehydration of diarrhea in infants. *J. Pediat.*, 28: 541, 1946.
29. HARRISON, H. E., TOMPSETT, R. R. and BARR, D. P. The serum potassium in two cases of sprue. *Proc. Soc. Exper. Biol. & Med.*, 54: 314, 1943.
30. HARRISON, H. E., HARRISON, H. C., TOMPSETT, R. R. and BARR, D. P. Potassium deficiency in a case of lymphosarcoma with the sprue syndrome. *Am. J. Med.*, 2: 131, 1947.
31. McCANCE, R. A. and WIDDOWSON, E. M. Alkalosis with disordered kidney function. *Lancet*, 2: 247, 1937.
32. MCQUARRIE, I. and WHIPPLE, G. H. Renal function influenced by intestinal obstruction. *J. Exper. Med.*, 29: 397, 1919.
33. TUCKER, W. J. Uremia following gastroenterostomy: eight cases. *Wisconsin M. J.*, 20: 528, 1922.
34. BINGER, C. A. L., HASTINGS, A. B. and NEILL, J. M. Edema associated with moderate bicarbonate administration during convalescence from pneumonia. *Arch. Int. Med.*, 31: 145, 1923.
35. STEELE, J. M. Renal insufficiency developing during prolonged use of alkalis. *J. A. M. A.*, 106: 2049, 1937.
36. McGEE, L. C., MARTIN, J. E., LEVY, F. and PERDUM, R. B. The influence of alkalosis on renal function. *Am. J. Digest. Dis.*, 6: 186, 1939.
37. ZEMAN, F. D., FREIDMAN, W. and MANN, L. T. Kidney changes in pyloric obstruction. *Proc. New York Path. Soc.*, 24: 41, 1924.
38. McLEITCHIE, N. G. B. Renal lesions in a case of excessive vomiting. *J. Path. & Bact.*, 55: 17, 1943.
39. MYERS, V. C. and BOOKER, L. E. Observations on the excretion of an acid urine in alkalosis. *Proc. Soc. Exper. Biol. & Med.*, 22: 512, 1925.
40. PITTS, R. F. and LOTSPEICH, W. D. Bicarbonate and the renal regulation of acid-base balance. *Am. J. Physiol.*, 147: 138, 1946.
- 40a. PITTS, R. F., AYER, J. L. and SCHEISS, W. A. The renal regulation of acid-base balance in man. II. The reabsorption and excretion of bicarbonate. *J. Clin. Investigation*, 28: 35, 1949.
41. SELLARDS, A. W. The determination of the equilibrium in the human body between acids and bases with especial reference to acidosis and nephropathies. *Bull. Johns Hopkins Hosp.*, 23: 289, 1912.
42. PALMER, W. W. and VAN SLYKE, D. D. Studies of acidosis: relationship between alkali retention and the alkali reserve in normal and pathological individuals. *J. Biol. Chem.*, 32: 499, 1917.
43. PALMER, W. W., SALVESEN, H. and JACKSON, H., JR. Relationship between the plasma bicarbonate and urinary acidity following the administration of sodium bicarbonate. *J. Biol. Chem.*, 45: 101, 1920.
44. PALMER, W. W. and HENDERSON, L. J. Clinical studies on the acid-base equilibrium: nature of acidosis. *Arch. Int. Med.*, 12: 153, 1913.
45. NADLER, C. S., BELLET, S. and LANNING, M. Influence of the serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. *Am. J. Med.*, 5: 838, 1948.
46. STEWART, H. J., SHEPARD, E. M. and HORGER, E. L. Electrocardiographic manifestations of potassium intoxication. *Am. J. Med.*, 5: 821, 1948.
47. TARAIL, R. Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances. *Am. J. Med.*, 5: 828, 1948.
48. BLISS, T. J. The acid-base composition of gastric juice during the secretory cycle. *Ann. Int. Med.*, 3: 838, 1930.
49. AUSTIN, J. H. and GAMMON, G. D. Gastric secretion after histamine: sodium and potassium content and pepsin estimation. *J. Clin. Investigation*, 10: 287, 1931.
50. SAEMUNDSSON, J. Potassium concentration in human gastric juice. *Acta med. Scandinav.*, Supp: 208, 1948.

Cardiopulmonary Function Studies in a Patient with Ligation of the Left Pulmonary Artery*

CHARLES E. ROH, M.D.,† DAVID G. GREENE, M.D.,‡ AARON HIMMELSTEIN, M.D.,
GEORGE H. HUMPHREYS III, M.D. and ELEANOR DEF. BALDWIN, M.D.

New York, New York

LIGATION of a right or left pulmonary artery has been performed many times and it is well known that the involved lung does not become fibrotic or gangrenous as long as the bronchial artery is left intact.¹⁻³ However, no report of physiologic studies under these circumstances has appeared until recently when Janton et al.⁴ published the results of bronchspirometric observations in a patient who had been subjected to a ligation of the pulmonary artery. The present report is concerned with similar but more extensive observations, including studies of cardiac function in a patient following ligation of the main left pulmonary artery.

CASE REPORT

A twenty-three year old Italian-American girl entered the Presbyterian Hospital in 1945, with the typical history, physical signs and laboratory findings of a *Streptococcus viridans* subacute endarteritis superimposed on a patent ductus arteriosus. Significant points in her past were history of a heart murmur, moderate physical limitation in a cardiac class during school years and inability to obtain a job because of the murmur. Her hospital course was complicated by bilateral pulmonary infarcts. No peripheral emboli were detected. Immediately following sterilization of her blood stream with parenteral penicillin, the patent ductus arteriosus was ligated but not severed.

Five months after a smooth postoperative

recovery and discharge from the hospital, recurrence of the machinery murmur which had disappeared following operation was noted. At this time several blood cultures revealed *Staphylococcus citreus*, and the patient was re-admitted to the hospital. Chest x-ray at this time disclosed enlargement of the left heart, dilatation of the pulmonary artery and increased vascular markings. (Fig. 1.) A pulmonary infarct in the left lower lobe was the only embolic phenomenon noted. After adequate penicillin therapy she underwent re-exploration. At operation an aneurysm communicating with both the aorta and the pulmonary artery was found at the site of the ductus arteriosus. In dissecting the aneurysm free from its attachment to the left pulmonary artery a tear occurred at the juncture of these two structures making it necessary to clamp and tie off the artery in order to control hemorrhage. The aneurysm was removed and the defects in the aorta and pulmonary artery were closed. The postoperative course was complicated by a left pleural effusion which subsided after a single thoracentesis, and by mild cardiac decompensation which responded well to digitalis.

At the present time, two years after the second operation, the patient is feeling well, has a normal exercise tolerance, and holds a full-time job as a sewing machine operator. Physical examination is entirely normal aside from a faint systolic murmur in the pulmonic area and a 4 cm. elevation of the left diaphragm. Fluoroscopic examination of her chest is essentially normal except for limited motion of the high left diaphragm. Chest x-ray (Fig. 2) shows con-

* From the Departments of Medicine and Surgery, College of Physicians and Surgeons, Columbia University, and the Cardio-Respiratory Laboratory of Presbyterian Hospital, New York, N. Y.

† At present at 576 Farmington Ave., Hartford 5, Conn.

‡ Fellow of the National Research Council in the Medical Sciences.



FIG. 1. X-ray taken before the second operation.

siderable decrease in the size of the cardiac silhouette and in the prominence of the vascular markings in comparison with her preoperative film.

METHODS OF STUDY

Pulmonary function was studied by the methods previously described.⁵ Vital capacity and maximum breathing capacity were measured on a recording spirometer, the residual air and the index of intrapulmonary mixing by the open circuit method. Pulmonary ventilation, pulmonary gas exchange and arterial oxygen saturation were determined during rest and the standard exercise test. The separate function of each lung was studied simultaneously by means of the Zavod catheter.⁶ Spirometric tracings were recorded and three-minute samples of expired air for measurement of minute ventilation and gas analysis were collected concurrently from both the right and left lungs.

Pressures were measured in the pulmonary artery and the chambers of the right heart by means of Hamilton manometers. The direct Fick method was employed to measure cardiac output.⁷



FIG. 2. X-ray taken two years postoperatively at the time of the physiologic studies.

RESULTS

Results of the pulmonary function study (Table 1) were within normal limits, except for hyperventilation and therefore a diminished rate of oxygen removal, under all conditions of observation. As may be seen from Table II and spirographic tracings (Fig. 3) obtained from each lung during bronchspirometry, the left lung, although normally ventilated, consumed a negligible amount of oxygen. In addition there was a slight reduction of the vital capacity of the left lung. The carbon dioxide output was diminished to a lesser degree than oxygen consumption as determined by direct analyses of the expired air. When this lung was ventilated by pure nitrogen, no change was noted in the arterial oxygen saturation, which remained 94 per cent. Cardio-circulatory studies (Table III) showed normal pressures in the pulmonary artery and chambers of the right heart. The cardiac index was high.

COMMENT

While pulmonary function studies were essentially within predicted limits, bronchspirometry revealed strikingly abnormal findings. The left lung, which has no

pulmonary arterial blood supply, is normally ventilated but participates only slightly in pulmonary gas exchange. The studies of Janton *et al.*⁴ in a similar case showed a diminished gas exchange in the affected left lung. They collected several

room air. They assumed that bronchial artery anastomoses with the pulmonary capillary bed could account for the oxygen and carbon dioxide values on the left side but found no available evidence to support this assumption.

TABLE I
RESULTS OF PULMONARY FUNCTION STUDIES

	Normal	Observed
i. Lung volumes in cc.		
Vital capacity.....	2975	2595
Residual air.....	745	620
Total capacity.....	3720	3215
Residual air/total capacity × 100.....	20	19
ii. Maximum breathing capacity in L./min.....	85	83
Ventilation in L./min./body surface m ²		
Rest.....	3.2 ± 0.4	4.3
Exercise.....	9.0 ± 1.7	13.0
Recovery first minute.....	10.9 ± 1.5	15.6
Recovery fifth minute.....	4.9 ± 0.6	5.9
Length of dyspnea in min- utes.....	0 — 1	1
iii. Index of intrapulmonary mix- ing (alveolar nitrogen per cent after 7 minutes oxygen breathing).....	<2.5	1.4
Arterial blood		
Oxyhemoglobin saturation per cent rest.....	96 ± 2	96.3
Oxyhemoglobin saturation per cent recovery first min- ute.....	96 ± 2	92.8
iv. Oxygen consumption in cc./ min./body surface m ²		
Rest.....	126 ± 2	141
Standard exercise.....	463 ± 76	526
Rate of oxygen removal in cc./ L. of ventilation		
Rest.....	45.1 ± 4.3	37.0
Standard exercise.....	60.2 ± 9.5	46.0

pairs of gas samples from the lungs functionally separated at the end of forced expirations. The samples from the left lung contained an average of 19.14 per cent of oxygen and 3.74 per cent of carbon dioxide. Since their catheter was sealed in place only during actual sampling, they postulated mixing of right and left lung air between periods of gas collection as the explanation for the observed difference between the gas content of the left lung samples and that of

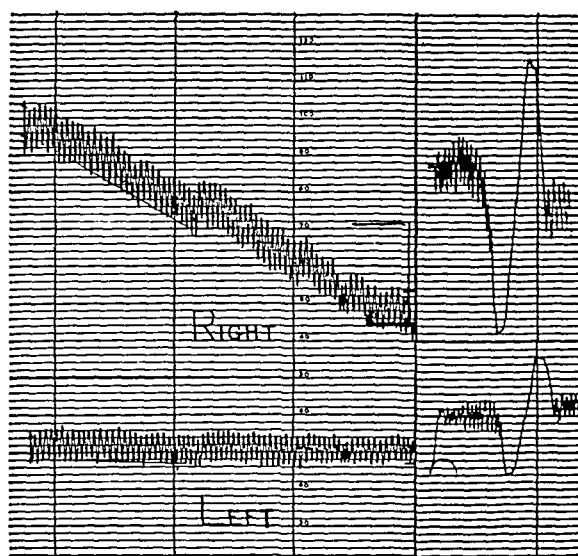


FIG. 3. Spirographic tracings of each lung. The vital capacity determination is to the right, the oxygen consumption and ventilation to the left.

In our studies the tip of the bronchial catheter was sealed in the left main bronchus throughout the procedure, eliminating mixing of air between the two lungs as the source of appreciable carbon dioxide output. Thus bronchial artery anastomoses with the pulmonary capillary bed could be shown to provide a reasonable explanation for the gas exchange observed in the left lung. This hypothesis most readily explains the fact that carbon dioxide output is greater than oxygen consumption. Since, as is well known, the carbon dioxide dissociation curve becomes steeper as the carbon dioxide tension becomes lower, a small gradient in carbon dioxide tension between the alveoli and pulmonary capillaries will result in a relatively large change in carbon dioxide volume. Consequently, even though the left lung was perfused entirely with arterial blood, an appreciable carbon dioxide output was observed. On the other hand, it is difficult for arterial blood to take up additional oxygen since the oxygen dissociation curve becomes flatter as higher

oxygen tensions are reached, requiring a high alveolocapillary gradient to add a small increment of oxygen to blood which is already almost fully saturated.

Simple diffusion through bronchiole walls is an alternative explanation for gas ex-

TABLE II
RESULTS OF BRONCHOSPIROMETRY

	Left Lung Per Cent of Total Function	
	Normal	Observed
Ventilation.....	35-50	37
Vital capacity.....	35-50	30
Oxygen intake.....	35-50	6
Carbon dioxide output.....	35-50	24

change in the left lung. Since carbon dioxide diffuses much more readily through tissues than oxygen, a disproportion in carbon dioxide and oxygen exchange would be anticipated. However, it seems highly unlikely that the latter mechanism could account for the relatively large amount of gas exchange observed in this patient.

The only abnormality observed in the pulmonary function study was hyperventilation associated with a decreased rate of oxygen removal at rest, during exercise and in the postexercise recovery period. In this respect our patient resembles a group of patients who had large air cysts which were poorly perfused with blood, yet were well ventilated by virtue of free communication with the tracheobronchial tree.⁸

SUMMARY

A case is reported in which cardiopulmonary function studies were performed on a patient two years after the left pulmonary artery was ligated. Cardiac catheterization revealed normal pressures in the pulmonary artery as well as in the chambers of the right side of the heart. The results of

pulmonary function tests were almost completely within normal limits. The only abnormalities found were a slight increase in cardiac index and hyperventilation under all conditions of observation. However, bronchspirometry disclosed a marked

TABLE III
RESULTS OF CARDIOCIRCULATORY STUDIES

	Normal	Observed
Pressures in mm. of mercury		
Pulmonary artery, systolic....	<30	23
Right ventricle, systolic.....	<30	24
Right auricle, mean.....	< 5	3
Cardiac index at rest		
(cardiac output, L./min./b.s. m ²).....	3.05 + 0.6	4.23

limitation of gas exchange in the left lung, with carbon dioxide output limited to a lesser degree than oxygen consumption. These findings are consistent with the assumption that anastomoses from the bronchial artery result in a considerable blood flow through the pulmonary capillary bed of the left lung.

REFERENCES

1. MEYER, W. On bronchiectasis. *Ann. Surg.*, 60: 7, 1914.
2. BROCK, R. C. Experiences in pulmonary artery ligation. *Guy's Hosp. Rep.*, 20: 217, 1940-41.
3. UGON, C. V. A., DE ESTABLE, M. C. and LOCKHART, J. Ligadura de la rama izquierda de la arteria pulmonar por hemoptisis grave. *Arch. urug. de med., cir. y especialid.*, 25: 230, 1944.
4. JANTON, O. H., REDONDO, H. P. and SCOTT, J. C. Pulmonary gas exchange following ligation of a pulmonary artery in man. *Federation Proc.*, 7: 61, 1948.
5. BALDWIN, E. DEF., COUNNAND, A. and RICHARDS, D. W., JR. Pulmonary insufficiency, I. Physiological classification, clinical methods of analysis, standard values in normal subjects. *Medicine*, 27: 243, 1948.
6. ZAVOD, W. A. Bronchspirometry, I. Description of the catheter and the technique of intubation. *J. Thoracic Surg.*, 10: 27, 1940.
7. COUNNAND, A., RILEY, R. L., BREED, E. S., BALDWIN, E. DEF. and RICHARDS, D. W., JR. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. *J. Clin. Investigation*, 24: 106, 1945.
8. Unpublished data.

Book Reviews

Syphilis. Its Course and Management. By Evan W. Thomas, M.D., 317 pages. New York, 1949. The Macmillan Co.

Dr. Thomas, who as visiting physician to the Bellevue Hospital and director of the Rapid Treatment Center there holds an authoritative position in his field, has written this book chiefly "to give busy individuals a practical understanding of the principles underlying the modern diagnosis and treatment of syphilis." The text accordingly is concisely organized, explicit in the details of diagnosis and treatment and full of illustrative case material. The point of view is wholly oriented toward the modern era of penicillin therapy, based upon an experience at the Rapid Treatment Center of 12,000 patients treated with penicillin in various dosage schedules.

Of the sixteen chapters three deal with etiology, immunology and the clinical course of the untreated disease; one is reserved for a discussion of quantitative serologic tests for syphilis; one (by Dr. T. J. Bauer of the U.S.P.H.S.) on public health aspects; one (and a short one at that) on iodides, bismuth, arsenicals and fever therapy, and the remainder cover the problems of early infectious syphilis, latent syphilis, late benign syphilis, cardiovascular syphilis, neurosyphilis, syphilis and pregnancy and congenital syphilis and their treatment with penicillin. Treatment schedules in current use are stated clearly but their provisional nature is stressed.

The exposition is in simple, direct style, the type is clear and well spaced, making for easy readability. The whole constitutes a comprehensible and up-to-date volume suited to the needs not only of the specialist but also of the student and general practitioner whose responsibility for diagnosis and treatment of syphilis is greater in the antibiotic age than ever before.

A.B.G.

Understandable Psychiatry. By Leland E. Hinsie, M.D., 359 pages. New York, 1948. The Macmillan Company.

The title of Dr. Hinsie's book is self-explanatory as to what he set out to

accomplish. His clear, delightful style of presentation has made a difficult subject "understandable" both to the medical profession and to the public. The material is well organized, modern and psycho-analytically oriented. The book should go a long way in taking the stigma out of psychiatry and psychiatric therapy. In Dr. Hinsie's attempt to simplify his subject matter he may have erred slightly on oversimplification, in that he symbolizes emotions, fears and anxieties a little too concretely. However, Dr. Hinsie has accomplished what he set out to do in a most pleasing manner.

S.M.D.

Coronary Heart Disease. By A. Carlton Ernstene, M.D., 86 pages. Springfield, Ill., 1948. Charles C. Thomas. Price \$2.50.

Dr. A. Carlton Ernstene of the Cleveland Clinic has written a concise, lucid compendium of the problem and management of the various aspects of heart disease due to derangement of the coronary artery circulation. His division of the subject into its various clinical manifestations is a useful one. Such a division inevitably results in a certain amount of overlapping since the underlying disorder is essentially the same. That he has adroitly avoided repetition is evident from the fact that the entire book, exclusive of bibliography, consists of only eighty-six pages. It should prove of interest and value to student and practitioner alike.

J.B.

The Renal Origin of Hypertension.* Harry Goldblatt, M.D., 126 pages. Springfield, Ill., 1948. Charles C. Thomas. Price \$2.75.

To Dr. Harry Goldblatt belongs the credit for proving that the kidney plays an important role in hypertension and for developing a successful method of producing this condition experimentally. His name has always been associated with carefully executed studies that have been amply confirmed.

Now, in monograph form, he has sum-

* Publication No. 14. In the American Lecture Series A Monograph in American Lectures of Pathology.

marized his investigations of the past two decades. These deal principally with the production of experimental renal hypertension by various means, the pathologic changes and mechanisms involved, the humoral mediators which participate and a brief summary of the similarities and differences between the experimental disease and its human equivalents.

Today there remain many unsolved problems concerning the part played by the kidney in hypertensive vascular disease and, indeed, serious doubts as to the function of renin and hypertensin as the humoral agents involved. There are no reservations about the major contributions of Dr. Goldblatt and the advance they have made to our knowledge. Lucidly written and attractively published, this volume is designed for those "whose interest is not sufficient to induce them to read the original papers or who do not have the time to devote to the reading of books on this subject." For this purpose it is an admirable addition to the many texts which have appeared on this important subject.

G.A.P.

General Endocrinology. By C. Donnell Turner, PH.D., 604 pages, Philadelphia, 1948. W. B. Saunders Co.

This textbook is designed primarily for college students with advanced biologic training although an effort is made to introduce correlations with clinical disease whenever possible. There is much in the way of fundamental information for the practitioner who wishes to acquire an anatomic and physiologic background. Unfortunately, the text suffers from the usual difficulty of being somewhat behind the

times; as for example, in the discussion of antithyroid drugs and their mechanism of action and in the omission of the more recent work with purified pituitary hormones.

On the whole, the book makes good reading but is not to be taken as a clinical text.

S.C.W.

Festschrift zum 80 Geburtstag Max Neuberger's. Vol. II, Wiener Beiträge zur Geschichte der Medizin. Edited by Dr. Emanuel Berghoff. pp. 491. Vienna, 1948. Wilhelm Maudrich. Price \$10.00.

This welcome volume is dedicated to Professor Max Neuberger, founder and head of the Vienna Institute for the History of Medicine and foremost medical historian of the day, upon the occasion of his eightieth birthday, December 8, 1948. The Festschrift is a collection of ninety-one essays on varied subjects of historical interest contributed by admirers, friends and former students, each choosing a topic of personal interest and writing in his own language. About one-third are in English, the remainder are chiefly in German and French. There are many quaint and interesting illustrations.

The essays are brief, some almost casual. Several deal with the etymology of certain medical terms, some with interesting medical personalities, places or manuscripts, some with episodes in the formulation of specialities, a few enter into philosophic considerations of historical development. All are interesting and enlightening, a tribute to Professor Neuberger's inspiration and influence. Even those who have no special interest in historical medicine will enjoy this volume for browsing and relaxation.

A.B.G.

AUTHOR INDEX VOLUME VI

- Adams, W. S., 141
 Alling, E. L., 141
 Askey, John Martin, 453
- Baker, A. B., 614
 Baldwin, Eleanor deForest, 24, 795
 Baldwin, Janet Sterling, 24
 Barnett, Roy, 522
 Barton, Harry C., Jr., 292
 Bauer, Theodore J., 341
 Bellet, Samuel, 712
 Bennett, Robert L., 620
 Bergman, H. C., 734
 Binger, Carl, 751
 Blake, William D., 470
 Bloomfield, Arthur L., 139
 Bodian, David, 563
 Bohnhoff, Marjorie, 417
 Bradley, Stanley E., 470
 Brown, John W., 321
 Buchthal, Fritz, 579
- Cantrell, James R., 345
 Carnes, William H., 3
 Cartwright, George E., 259
 Cathcart, Richard T., 725
 Clifford, Jack E., 321
 Conan, Neal J., Jr., 309
 Courmand, André, 24, 725
- Deitrick, John E., 684
 de Vries, A., 51
 Dorset, Virgil J., 135
 Dresdale, David T., 530
 Dunning, Marcelle F., 790
- Eisenberg, Henry, 449
- Ferrer, M. Irené, 725
 Fleischner, Felix G., 756
 Fletcher, D. E., 177
 Franklin, Murray, 278
 Frazier, Chester N., 443
- Gazes, Peter C., 712
 Gellhorn, Alfred, 188
 Gibson, Count Dillon, 41
 Goldman, Melvin L., 162
 Goodman, Edmund N., 168
 Green, William T., 606
 Greene, David G., 24, 795
 Gubner, Richard, 60
 Gucker, Thomas, 606
- Hanger, Franklin M., 275
 Harding, Floyd E., 329
 Harvey, Réjane M., 725
- Hatch, Francis N., 633
 Higgins, William H., Jr., 3
 Himmelstein, Aaron, 24, 795
 Hoffman, William S., 433
 Holmes, Hilary H., 398
 Holmes, Robert O., 3
 Horns, Howard L., 272
 Horstmann, Dorothy M., 592
 Howe, Howard A., 537
 Humphreys, George H., 795
- Iskrant, Albert P., 341
 Israel, Harold L., 745
- Jones, Logan O., 188
- Keefer, Chester S., 405
 Kennedy, Richard J., 672
 Kennedy, Thomas J., Jr., 790
 Kinsell, Laurance W., 292
 Kneeland, Yale, Jr., 41
 Knight, Vernon, 407
 Kozoll, Donald D., 278
- Lanning, Mary, 712
 Lawrence, J. S., 141
 Luisada, Aedo A., 756
- Maher, Irene E., 745
 McDermott, Walsh, 407
 McMichael, John, 651
 Melcher, George, 398
 Merrill, Arthur J., 357
 Messinger, William J., 168
 Meyer, Karl A., 278
 Michael, Max, Jr., 462
 Michaels, George D., 292
 Miller, C. Phillip, 417
 Molner, Joseph G., 628
 Morgan, Isabel M., 556
 Murphy, Louis R., 672
- Nadler, Carl S., 712
 Nobe, Catherine, 433
 Noble, Charles A., Jr., 3
- Paine, Robert, 84
 Paul, John R., 535
 Perez-Pina, Florentino, 530
 Pian, H. C., 443
 Plotke, Frederick, 449
 Pomeranc, Mark, 433
 Popper, Hans, 278
 Prinzmetal, M., 734
- Rachmilewitz, M., 51
 Randall, Elizabeth, 424
- Rantz, Helen H., 424
 Rantz, Lowell A., 424
 Ravitch, Mark M., 345
 Reisner, Edward H., Jr., 643
 Relman, Arnold S., 522
 Richards, Dickinson W., Jr., 772
 Richards, Victor, 633
 Rigdon, R. H., 177
 Roh, Charles E., 24, 795
 Rose, Harry M., 41
 Ruiz-Sanchez, Amado, 407
 Ruiz-Sanchez, Francisco, 407
- Sadusk, Joseph F., Jr., 522
 Schittone, M., 513
 Schroeder, Henry A., 162
 Schumert, M., 51
 Schwartz, S., 513
 Selzer, Arthur, 3
 Shaver, John S., 292
 Shorr, Ephraim, 684
 Siddon, W. H., 177
 Simkin, Benjamin, 734
 Sims, John LeRoy, 321
 Smith, John R., 84
 Snyderman, Ruben, 336
 Spain, David, 530
 Spiegl, Ralph J., 633
 Spitz, H., 513
 Stead, Eugene A., Jr., 232
 Steigmann, Frederick, 278
 Steinbrocker, O., 513
- Terry, Luther L., 135
 Tipping, James S., 336
- Ungerleider, Harry E., 60
- van Dyke, H. B., 681
 Volini, Italo F., 433
- Wagner, Robert R., 522
 Ward, Robert, 551
 Webster, Maric B., 745
 Weiner, Herbert M., 725
 Weiss, Harry A., 292
 Wells, E. Buist, 267
 West, Randolph, 643
 Whedon, G. Donald, 684
 White, Edward, 321
 White, James C., 168
 Winkley, John H., 790
 Womack, C. Ray, 267
- Youmans, John B., 1

SUBJECT INDEX VOLUME VI

(E.) = Editorial

Abstracts

- of papers of American Federation for Clinical Research, 504, 662
- of papers of Western Society for Clinical Research, 386
- Adrenal medullary tumor, 633
- Alkalosis, gastric, with hypokalemia, 790
- Amebiasis, hepatic, treatment of, with chloroquine, 309
- American Federation for Clinical Research, 504, 662
- Analgesic drugs, synthetic (E.), 681
- Anemia, 125
 - pernicious, treatment of, 643
- Anorexia, weakness, prostration and death, 495
- Antibiotics (E.), 405
- Arteriosclerosis, 60
 - and cholesterol metabolism, 103
- Aspirin, in treatment of rheumatic fever, 433
- Aureomycin
 - in atypical pneumonia, 41
 - in typhus and brucellosis, 407

- ## Bacterial flora of throat, effect of streptomycin on, 417
- Blood and plasma transfusion, in transmission of disease, 345
 - Book reviews
 - Acute Bacterial Diseases—Their Diagnosis and Treatment (Dowling, Sweet and Hirsh), 534
 - Coronary Heart Disease (Ernstene), 799
 - Festschrift zum 80 Geburtstag Max Neuberger's (Berghoff), 800
 - General Endocrinology (Turner), 800
 - Renal Origin of Hypertension (Goldblatt), 799
 - Syphilis, Its Course and Management (Thomas), 799
 - Understandable Psychiatry (Hinsie), 799
 - Brucellosis, aureomycin in, 407

Cardiac

- failure with hemosiderosis of myocardium, 272
- output in congestive heart failure, 232
- venous congestion, 651
- Cardiopulmonary function studies, 795
- Cardiovascular failure, 84
- Cerebrospinal fluid, infectivity of, in secondary syphilis, 443
- Chemotherapy of malignant disease, 188
- Chiari's syndrome, 398
- Chloroquine in treatment of hepatic amebiasis, 309
- Cholesterol metabolism and arteriosclerosis, 103
- Clinic on psychosomatic problems (Massachusetts General Hosp.)

- A case of duodenal ulcer with anxiety attacks treated by psychotherapy, 368
- Clinico-pathologic conferences (Washington Univ.)
 - Anorexia, weakness, prostration and death, 495
 - Hepatosplenomegaly, jaundice, anemia and recurrent fever, 125
 - Mediastinal tumor with gynecomastia and superior vena caval obstruction, 247
 - Pneumonia and empyema, 375
 - Rheumatic heart disease with respiratory failure, 781
- Clonorchiasis with eosinophilia and pulmonary infiltrations, 259
- Colitis, ulcerative, 481
- Columbia combined staff clinics
 - Cholesterol metabolism and arteriosclerosis, 103
 - Ulcerative colitis, 481
- Combined staff clinics (Columbia Univ.)
 - Cholesterol metabolism and arteriosclerosis, 103
 - Ulcerative colitis, 481
- Conferences on therapy (Cornell Univ.)
 - Household poisonings, 237
- Congestive heart failure, dynamics of, 772
- Cornell conferences
 - Household poisonings, 237
- Coronary arteritis, (E.), 139
- Coronary circulation, 734

- ## Diabetes and pheochromocytoma, 51
- Duodenal ulcer, psychotherapy in, 368

Electrokymography, 756

- Electrophoretic abnormalities of multiple myeloma, 141
- Empyema and pneumonia, 375
- Endocarditis, subacute bacterial, 336
- Endocrinopathies in hyperostosis frontalis interna, 329
- Endophlebitis, obliterative, of hepatic veins, 398
- Eosinophilia, with clonorchiasis, 259

Fluorocardiography, 756

- Foramen ovale, patent, and pulmonary stenosis, 3
- Friedländer's bacillus meningitis treated with streptomycin, 522

Glanders, chronic, and multiple cystic osseous tuberculosis, 267

- Glomerulonephritis and tonsillectomy, 462
- Gout, fulminating, fatal, 513
- Gynecomastia, 247

Heart

- block and leukemic cell infiltration, 530
- failure, 84
 - congestive, and renal dysfunction, 470
 - cardiac output in, 232
 - salt and water retention in, 357
- Hemochromatosis, 272
- Hemopneumothorax, spontaneous, 135
- Hemosiderosis of myocardium, 272
- Hepatic disease, problems of (E.), 275
 - veins, endophlebitis of, 398
- Hepatosplenomegaly, 125
- Histamine in test for hypertensive diencephalic syndrome, 162
- Hyperostosis frontalis interna in endocrinopathies, 329
- Hypertension and pheochromocytoma, 51
- Hypertensive diencephalic syndrome, test for, using histamine, 162
- Hypokalemia, with gastric alkalosis, 790

Immobilization, effects of, on metabolic and physiologic functions, 684

Immunization with group A hemolytic streptococci, 424

Infarction

- myocardial, 734
 - auricular flutter in, 453
- Intestinal obstruction, vomiting due to, 712

Jaundice, 125

Leukemic cell infiltration of heart, 530

Liver

- function and structure of, 278, 292
- during infectious mononucleosis, 321

Malignant disease, chemotherapy of, 188

Massachusetts General Hosp. clinic on psychosomatic problems

- A case of duodenal ulcer with anxiety attacks treated by psychotherapy, 368

Mediastinal tumor, with gynecomastia and superior vena caval obstruction, 247

Medical history, 751

Meningitis, Friedländer's bacillus, 522

Mononucleosis, infectious, liver function during, 321

Myeloma, multiple, electrophoretic abnormalities of, 141

Myocardium, cardiac failure with hemosiderosis of, 272

Nephritis, glomerular, and sulfonamide sensitivity, 177

Oscillating bed, use of, in immobilization, 684

Penicillin in oil and beeswax in treatment of syphilis, 449

Pheochromocytoma, 633

- with diabetes and hypertension, 51

Pneumonia

- and empyema, 375
- aureomycin in treatment of, 41

Poisonings, household, 237

Poliomyelitis

- acute, clinical aspects of, 592
- after effects of, 620
- bulbar, mechanism and treatment of, 614
- clinical findings in, 563
- epidemiology of, 537
- immunity in, 556
- moist heat in treatment of, 606
- pathologic physiology of, 579
- public health considerations in, 628
- symposium, foreword, 535
- viruses of, 551

Pulmonary

- artery, ligation of, 795
- stenosis and patent foramen ovale, 3
 - congenital, and idiopathic dilatation of pulmonary artery, 24

Recurrent fever, 125

Renal dysfunction during congestive heart failure, 470

Respiratory failure, with rheumatic heart disease, 781

Rheumatic fever

- and tonsillectomy, 462
- treatment of, with aspirin, 433
- heart disease with respiratory failure, 781

Salt and water retention in heart failure, 357

Seminars on congestive failure

- Cardiac venous congestion, its causes and consequences, 651
- Dynamics of congestive heart failure, 772
- Mechanism of heart failure. A résumé of physiologic factors in cardiovascular failure, 84
- Mechanisms of salt and water retention in heart failure, 357
- Pathogenesis of renal dysfunction during congestive heart failure, 470
- Role of the cardiac output in the mechanisms of congestive heart failure, 232

Serum

- mucoprotein, changes in, following myocardial infarction, 734
- polysaccharide determinations, 745
- potassium, effect of vomiting on, 712
- protein values (E.), 1

Streptococcal throat, and tonsillectomy, 462

Streptococci, group A hemolytic, immunization with, 424

Streptomycin

- effect of, on bacterial flora of throat, 417
- in Friedländer's bacillus meningitis, 522
- in glanders and osseous tuberculosis, 267

Sulfonamide sensitivity and glomerular nephritis, 177

Sympathectomy in thromboangiitis obliterans, 168

Symposium on poliomyelitis, 535

Syphilis

epidemiology of, 341

penicillin in oil and beeswax in treatment of, 449

secondary, infectivity of blood and cerebrospinal fluid in, 443

Tachycardia, in Wolff-Parkinson-White syndrome, 725

Thromboangiitis obliterans, 168

Tonsillectomy for streptococcal sore throat, rheumatic fever and glomerulonephritis, 462

Transfusion of blood and plasma, transmission of disease by, 345

Tryptophane-Perchloric acid reactions in polysaccharide determinations, 745

Tuberculosis, osseous, and chronic glanders, 267

Typhus, aureomycin in, 407

Ulcer, duodenal, treated by psychotherapy, 368

Vena caval obstruction, 247

Vitamin B₁₂, crystalline, in pernicious anemia, 643

Vomiting due to intestinal obstruction, 712

Washington Univ. clinico-pathologic conferences

Anorexia, weakness, prostration and death, 495

Hepatosplenomegaly, jaundice, anemia and recurrent fever, 125

Mediastinal tumor with gynecomastia and superior vena caval obstruction, 247

Pneumonia and empyema, 375

Rheumatic heart disease with respiratory failure, 781

Weber-Christian disease, 672

Western Society for Clinical Research, 386

Wolff-Parkinson-White syndrome, 725

